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THRESHOLD ERYTHEMA DOSE OF ROENTGEN RAYS

II. AN EXPERIMENTAL INVESTIGATION OF VARIOUS ASPECTS OF THE ERYTHEMA REACTION AND A NEW CLINICAL CRITERION FOR THE STANDARD THRESHOLD ERYTHEMA REACTION

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In the first paper [1] of this series Pugh and I reported the results of an investigation of the various magnitudes of the dose in roentgens reported in the literature as being equivalent to the erythema dose and also the variation in this dose in actual clinical use in Australia, the United States and England.

In order to obtain a more complete picture of the various clinical aspects of the erythema reaction the extensive experimental program herein reported was carried out.

A new criterion of the threshold erythema reaction is proposed and defined, which, it is believed, would greatly increase the degree of accuracy with which different workers could correlate their observations by avoiding the necessity for judging the degree of the reaction. A number of tests were performed before a suitable portion of the body could be chosen as a standard location for the tests, and the question of the effect of the quality of the radiation was also investigated.

The results of four hundred and eighty tests on 40 different subjects were analyzed with respect to coloring, sex, age and texture of the skin. To the best of my knowledge tests of the cutaneous reaction on infants in sufficient numbers to enable statistical conclusions to be drawn have not previously been reported; 21 infants between the ages of 3 weeks and 6 months were tested, and the conclusions are reported.

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1. Belisario, J. C., and Pugh, R. E., Jr.: Threshold Erythema Dose of Roentgen Rays: I. Review of the Literature and Comment on Variation of Doses in Use in Australia, the United States and England, Arch. Dermat. & Syph. **45**:519 (March) 1942.

Special, controlled tests were devised to attempt to determine the answers to some of the questions which have arisen in many of the articles in the literature, as well as in the results of the present experimental program. These special investigations included further contributions regarding the causes which have been suggested for both the primary and the secondary erythema reactions, the relative value of erythema and epilation tests, the rate of recovery as determined clinically, the effect of the intensity or rate of application of the dose and the effects of ultraviolet and infra-red radiation administered immediately prior to exposure to roentgen rays. The results of the latter test indicated possible clinical use of such combined irradiation, and this possibility is discussed. Tissue injury is shown to be a factor of importance in the irradiation of large areas.

DEFINITION AND CRITERION OF THE THRESHOLD ERYTHEMA DOSE

On the basis of experiments performed, the threshold erythema dose is defined as *the minimal amount of roentgen radiation which will produce an erythema or pink reaction (whether mottled or homogeneous) within nine to fourteen days, with a sharply defined complete edge, over a circular area 1 cm. in diameter on the upper anterior covered portion of the thigh.*

This reaction is produced in approximately 80 per cent of persons from the age of 10 years upward by a dose of 350 r when the radiation has a half value layer of 0.9 mm. of aluminum. For this investigation the technic factors were: 110 kilovolts, 6 milliamperes, 20 cm. target-skin distance, no added filter, a half value layer of 0.9 mm. of aluminum and an intensity of 360 r per minute, measured in air, without back scatter. A circular area 1 cm. in diameter was chosen as being the largest area of convenient size which was unaffected to an appreciable extent by back scatter. The areas most commonly employed by other investigators (i. e., a circle 1 inch [2.5 cm.] in diameter or a field 1 inch square), have approximately 11 or 12 per cent back scatter (Quimby, Marinelli and Farrow [2]) to be considered.

AREA OF THE BODY MOST SUITABLE FOR TESTS ON ADULTS

Before the covered portion of the anterior upper aspect of the thigh was selected as the area for the tests, a number of exposures were made with circular apertures both 1 and 2.5 cm. in diameter on the flexor surfaces of the forearm and upper part of the arm, the abdomen, the chest and the upper and lower portions of the anterior aspect of the thigh. These tests showed the sensitivity, or the degree of pink reaction,

2. Quimby, E. H.; Marinelli, L. D., and Farrow, J. H.: A Study of Back-scatter, Am. J. Roentgenol. **39**:799, 1938.

to be greatest on the abdomen and progressively less in the following sites: (*a*) abdomen, (*b*) flexor surface of the forearm (in an untanned person), (*c*) upper anterior covered portion of the thigh, (*d*) flexor surface of the arm, (*e*) chest and (*f*) lower anterior aspect of the thigh. This order applies in the majority of cases only if the arms have not been sufficiently subjected to sunlight for the production of even mild pigmentation.

In Australia sun bathing and swimming and the wearing of short sleeves and short trousers or trunks are so much in vogue that the arms and lower portions of the thighs are almost always noticeably pigmented. Consequently the anterior covered portion of the upper part of the thigh was chosen, as this area would give the most uniform and representative results, being unpigmented from the sunlight in almost all persons. Pigmentation due to sunlight was invariably found to diminish the degree of pure erythema reaction, even though at first glance these areas appeared in some instances to be redder than the unpigmented ones after exposure to roentgen rays. This was found on closer examination to be due to the combined effects of pigment and erythema, not to erythema alone.

ARRANGEMENT OF APERTURES FOR THE TEST EXPOSURES

Altogether four hundred and eighty circular areas 1 cm. in diameter on the normally covered portion of the upper anterior aspect of the thigh in 40 persons were exposed to roentgen rays. In all cases both thighs were irradiated, as shown in the diagram. In the preliminary trials five areas, each 1 cm. in diameter, were arranged in the form of a square with one area at the center; the four outer circles were arranged with their margins just 3 mm. from the margin of the central area. The doses given were 250, 300, 350, 400 and 450 r. Then it was considered that possibly the primary reaction might appear in some cases with less than 250 r; so six areas were used in the final tests, arranged as shown in figure 1. Twenty subjects were exposed according to figure 1*a* and 20 according to figure 1*b* to avoid any possibility of asymmetry in irradiation or reaction. The long axis of each group of six circles was placed parallel to the long axis of the thigh.. Three millimeters of tissue was left unexposed between the margin of each circle and that of its immediate neighbor. The circles were cut in a sheet of a tin and lead compound material 0.5 mm. thick, with a standard circle punch 1 cm. in diameter.

All areas in the group were irradiated with the minimum dose to be employed in the series; then they were covered in succession, and 50 r more was delivered successively to the remaining areas until the maximum dose for the series was given to the last area exposed. The metal sheet was strapped to the thigh with adhesive plaster to avoid movement, and a lead-glass applicator was used to localize the x-ray

beam. Since the whole six areas were so close together on each thigh, on the flattest surface available, they could be covered with a cone or applicator only 2 inches (5 cm.) in diameter, and the effect of the inverse square law with regard to the distance from the focal spot to each of the areas was negligible.

It is suggested that if the threshold erythema dose is defined as the minimum dose in roentgens which will produce a pink coloration within a circle 1 cm. in diameter with a sharply demarcated complete outline

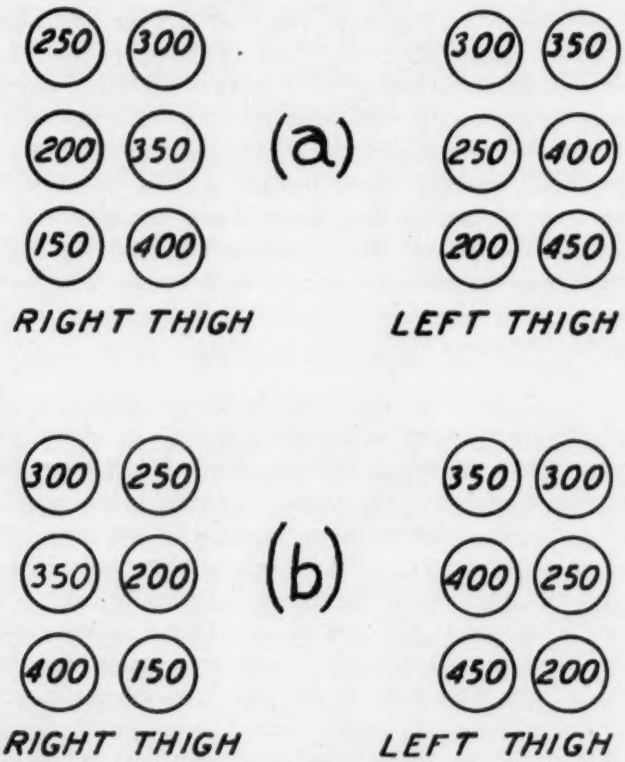

Fig. 1.—Arrangement of apertures for the erythema dose test exposures. Twenty of the patients were given radiation according to arrangement (*a*) and according to (*b*), to avoid any possibility of asymmetry in irradiation or reaction (actual size). Each aperture was 1 cm. in diameter, with 3 mm. between the edges of the adjoining circles. Doses are given in roentgens.

(whether the center is mottled or homogeneous), it will eliminate the variation in judgment of different observers as to the degree of pinkness required. This would greatly increase the degree of accuracy with which different investigators could correlate their standards, as differences in the color perception of various persons would not create the discrepancy noted in present records of erythema tests.

The exposed areas were examined in daylight in a well lighted room with the subject first lying down and then standing up. Direct light was allowed to fall on the areas, and then they were shaded with a thin sheet of cardboard in order to be sure of the sharp outline of the area, which is regarded as the criterion of the threshold erythema reaction. Firm pressure with a glass slide was made over the exposed areas during the examination, as this obliterates plain erythema but not pigmentation. In this way changes from an erythema reaction to pigment formation were more easily noted.

IMPORTANCE OF THE THRESHOLD ERYTHEMA REACTION

Prior to the general use of ionization chambers for the measurement of roentgen ray dosage, the Sabouraud-Noiré pastille and erythema tests were practically the sole guides for determination of dosage. Now that ionization measurements are becoming more and more accurate and universally identical and have replaced the pastilles, the tendency is to disregard tests of the skin entirely. This is more noticeable among radiologists than among dermatologists, particularly in the treatment of cutaneous lesions. Since most of the radiologist's work is with deep-seated malignant lesions, his primary concern is to destroy the neoplasm, without particular regard for the resultant cosmetic appearance. This idea is also applied in the cases of small basal cell or squamous cell epitheliomas, whereas in such cases, by the nature of his practice, the dermatologist must consider the final cosmetic result as well.

Consequently, since the threshold erythema dose is still the only biologic test available, it should be performed whenever possible to determine the sensitivity of the subject to roentgen rays. Different persons may vary considerably in the reactivity of their skin to roentgen rays, as manifested by their erythema reaction, and an approximate estimate of their tolerance can be gained by the performance of cutaneous tests. These should still be considered a necessary part of dosage determination.

Actual erythema reactions were chosen as the best standard for this paper, rather than the pigmentation reactions of Quimby, for the following reasons:

(*a*) The dilatation of the blood vessels is an earlier reaction than pigment formation; pigmentation may occur as an effect of roentgen rays, sunlight, minute trauma, friction and even some constitutional diseases without erythema having been visible to the naked eye.

(*b*) It has been found by numerous investigators (e. g., MacKee, Cipollaro and Niles) that in the treatment of acne vulgaris, pigmentation may occur during treatment, but permanent after-effects and damage, in the form of discolorations or telangiectases, do not occur unless

erythema has been produced during the cycle of treatments. My own experience supports these observations as well. It seems, therefore, that the erythema reaction is a more accurate indication of possible after-damage to the skin than the pigmentation dose. In other words, pigmentation may be more suitable for accurate determination of borderline visible biologic reaction and its correlation with other methods of intensity measurement, but actual erythema reaction is more valuable as a clinical measure of tolerance or future damage.

If these facts are borne in mind, it would appear that a statement made by Paterson [3] is hardly tenable, at any rate in therapy of the skin. He stated:

> The erythema dose had a right to survive only so long as there were no better instruments for measuring quantity of radiation. This lack has been filled by the modern ionization chamber. In actual practice today, the so-called erythema dose is found to mean little more than a fixed period of exposure at certain fixed plant factors.

This statement typifies the radiologist's point of view in contradistinction to that of the dermatologist, who realizes that the cutaneous test is still the only biologic test and must still be employed in conjunction with ionization methods. Obviously the problems in the fields of deep (high voltage) roentgen therapy and superficial (low voltage) roentgen therapy of the skin are not the same, but dermatologists must keep this fact in mind when such statements are made.

(*c*) A third reason for choosing the erythema reaction in preference to the pigmentation reaction is that the former is an effect on the blood vessels, destruction or damage to which is causative of later cutaneous effects and the possibility of permanent damage. The pigmentation reaction is mainly an effect on the pigment-forming cells of the epidermis and gives no definite indication of possible later damage to the skin.

THE EFFECT OF QUALITY OF THE RADIATION (ESPECIALLY FILTRATION)

Two hundred tests were performed on 20 subjects to determine the approximate difference in the number of roentgens required to produce a threshold erythema reaction when filters of 0, 1, 2 and 3 mm. of aluminum were used, all other factors remaining constant. A Philips Metalix tube and an Acme "660" mechanical rectifier were used. The inherent filtration of the x-ray tube was approximately 0.3 mm. of aluminum. Operating technic factors were: 110 kilovolts, 6 milliamperes, 20 cm. target-skin distance, 360 r per minute, in air, without added filter, and a half value layer of 0.9 mm. of aluminum. The

3. Paterson, R.: The Value of Assessing and Prescribing Dosage in Radiation Therapy in Simple Terms, Radiology **32**:225, 1939.

threshold erythema dose in roentgens was first determined for each subject without added filter, and this dose was then delivered at the same time as the tests with filtered radiation, as a control.

Figure 2 shows the arrangement of the apertures for the filtered radiation tests; doses of 350, 400 and 450 r were delivered with 1 mm. of aluminum, 400, 450 and 500 r with 2 mm. of aluminum and 450, 500 and 550 r with 3 mm. of aluminum. The clinical appearances obtained from these exposures were compared with that of the unfiltered erythema dose exposure of 350 r. All tests were made on the upper, normally covered, anterior aspect of the thigh of the subject. The exposed areas were all within a circle covered by an applicator or cone 2½ inches (6 cm.) in diameter, so the effect of the different distances from the target to the various areas was negligible.

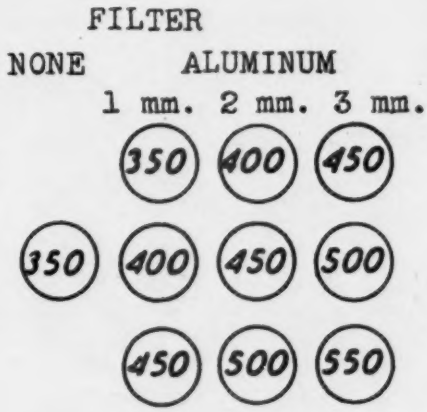

Fig. 2.—Arrangement of apertures for tests of the effect of filtration on the erythema dose reaction. Each aperture was 1 cm. in diameter, with 3 mm. between the edge of adjoining circles (actual size). Doses indicated are in roentgens.

Although some variations occurred, in approximately 80 per cent of the cases the threshold erythema dose without added filter was produced by 350 r. With 1 mm. of aluminum as added filter, 400 r was required for the threshold erythema dose; with 2 mm. of aluminum as added filter, 450 r gave the threshold erythema reaction, and with 3 mm. of aluminum added, the threshold erythema dose was 500 r. From these tests it is apparent that approximately 50 r more was required for each additional 1 mm. of aluminum filter.[4]

4. Through an oversight the half value layers were omitted in the discussion of the effect of filtration on the erythema dose. After considering all the data available and comparing with a similar Philips Metalix tube operating with a mechanical rectifier, I found that the following values closely approximate the

(Footnote continued on next page)

It was noted that the time at which both the primary and the secondary erythema reactions appeared was delayed and that the duration of the reaction was shortened for each additional unit of filtration added. This was more noticeable in the secondary than in the primary reaction, the latter being much less affected. These observations are consistent with the theory that the greater the filtration, and consequently the penetration, the less is the absorption of the primary beam in the layers of skin. When larger areas are exposed and doses greater than the threshold erythema dose are given, a converse effect is observed; with higher voltage and greater filtration the cutaneous effects last comparatively longer and tend to increase proportionately in degree of redness when compared with lower voltage unfiltered radiation, due to deeper tissue damage. The higher voltage and greater filtration used for noting this effect, however, are outside the range in use for therapy of the skin, and the comparison has no practical value in clinical dermatology. The fact that the same phenomenon may be noticed with unfiltered radiation for larger fields, however, has some significance and will be discussed in more detail in the section of this paper under "volume or tissue injury." Some of the confusion in the magnitude of the erythema dose and in the comparative effects of filtered and unfiltered radiation has resulted from ignoring the separate effects involved in deep and in superficial roentgen therapy and trying to apply the results in both fields to clinical dermatology. Erskine [5] noted that greater doses of higher kilovoltage filtered radiation were necessary than for lower voltage unfiltered radiation, to produce equal cutaneous reactions and, further, that the skin would recover from larger doses of the low voltage, soft radiation than from harder radiation, owing to the fact that the latter irradiation did more damage to subcutaneous tissues. Reinhard [6] assumed that the difference in the dose required to produce an erythema reaction with radiation of different qualities was due to decreased absorption by the skin in the case of the harder radiation. Andrews [7] reported the

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quality of radiation actually used, and for universal comparison of the effect of quality they should be used in preference to the somewhat ambiguous added filter values: For no added filter, a half value layer of 0.9 mm. of aluminum (this is an actual value reported in the paper); for 1 mm. of aluminum added, 2 mm. of aluminum; for 2 mm. of aluminum added, 2.5 mm. of aluminum; for 3 mm. of aluminum added, 3 mm. of aluminum. If smaller steps were used in the erythema tests with varying filtration, the curve would possibly be found to be linear with respect to half value layer. (Note added by Robert E. Pugh Jr.)

5. Erskine, A. W.: Quality Versus Erythema, in Practical X-Ray Treatment, St. Paul, Bruce Publishing Company, 1931.

6. Reinhard, M. D.: Variations in Dosage Dependent upon Wave Length, Am. J. Roentgenol. **31**:538, 1934.

7. Andrews, G. C.: Diseases of the Skin, ed. 2, Philadelphia, W. B. Saunders Company, 1938.

erythema dose for the usual quality used in dermatologic work as 350 r with valve rectification, 400 r with mechanical rectification and 500 r for 135 kilovolts and 3 mm. of aluminum; for 200 kilovolts (high voltage therapy) it was about 600 r. The trend of these values is in the same direction as found in the present experiments. Schwarz and others in studying the effects of different qualities of radiation used 1,000 r as the dose; under such conditions it is feasible that the harder radiation produced the more pronounced reaction but not under the same conditions as obtain for threshold erythema tests. With such large doses "volume effect" or deeper tissue injury plays the preponderant part, while for threshold erythema doses absorption in the layers of skin themselves is the principal cause of reaction.

SUMMARY OF THRESHOLD ERYTHEMA TESTS ON ADULTS

The statistical results of the four hundred and eighty test exposures on 40 subjects are collected and summarized in table 1. These tests were made with unfiltered radiation and constitute the principal investigation of this experimental program. Sixty other subjects were also tested, but, owing to their inability to attend regularly for observation as required, the data on them are not included in the summary, although much useful information on other aspects was obtained. The 40 subjects reported on were observed regularly from the time of the application of the radiation until the disappearance of the cutaneous reactions.

In all the cases the subjects were exposed to the radiation between 9 and 10 a. m., and they were instructed to observe the areas irradiated hourly, commencing two hours after the application. They returned for observation six hours after irradiation; this early observation has apparently been rarely performed by other investigators, as so little is heard or written about the primary erythema, or first wave, reaction, which occurs in approximately the same number of cases as the secondary, or second wave, reaction.

The information in table 1 is more or less self explanatory, and only certain aspects and indications which seem worthy of notice will be discussed under their various headings.

Total Number of Subjects Tested.—Of the subjects tested, 80 per cent showed a primary erythema reaction which appeared within five to eleven hours after irradiation; 20 per cent did not exhibit this reaction. If a primary reaction occurred at all in a subject no more than 250 r was required to evoke it; in the case of the secondary erythema reaction, 450 produced the reaction in 100 per cent of the cases, and 250 r was the minimum which ever produced this, the usually observed, type of erythema. Of the 32 subjects who showed the primary, or early, erythema, 22 (69 per cent) required only 200 r and 10 (31 per cent) reacted to 250 r. In 16 (50 per cent) of these 32 subjects, the

TABLE 1.—*Results of Threshold Erythema Tests in Adults*

Groups of subjects							Sex		Age			Texture of Skin		
Hair / Complexion / Texture of skin	Red Fair, red	Fair Fair	..... Brunette	Dark Fair	Dark Medium	Dark Coarse	Male	Female	10 to 18 Years	19 to 35 Years	36 to 75 Years	Fine to Medium	Coarse, Greasy	Totals
Total number of cases in each group	7	6	5	4	8	10	15	25	12	13	15	20	20	40
Primary erythema reaction (appearing five to eleven hours after irradiation)														
Showed reaction														
Number	6	6	4	4	7	5	10	22	12	13	7	20	12	32
Per cent of total group	86	100	80	100	88	50	67	88	100	100	47	100	60	80
No primary erythema														
Number	1	0	1	0	1	5	5	3	0	0	8	0	8	8
Per cent of total group	14	0	20	0	12	50	33	12	0	0	53	0	40	20
Time of appearance (hours)														
Range	5 to 9	6 to 9	6 to 10	5 to 10	6 to 8	6 to 11	7 to 9	5 to 11	5 to 11	5 to 10	5 to 10	5 to 10	6 to 11	5 to 11
Average	6.9	7.5	8.1	7.0	7.6	7.7	7.8	7.3	7.3	6.8	7.2	7.2	7.7	7.4
Period of duration (hours)														
Range	1 to 9	1 to 8	3 to 9	....	1 to 10	3 to 9	1 to 5	1 to 10	1 to 9	4 to 10	1 to 5	1 to 8	1 to 10	1 to 10
Average	4.6	3.75	5.5	....	5.5	5.8	3	5	5.2	7.5	2.3	5	5	5
Cases in which primary reaction persisted into secondary erythema without subsiding														
Number	2	2	1	4	5	2	5	11	5	8	3	12	4	16
Per cent of cases which showed primary reaction	33	33	25	100	71	40	50	50	42	62	43	60	33	50
Minimum dose for primary erythema reaction (number of cases for each dose)														
200 r	5	5	3	2	4	3	7	15	8	8	6	X	X	22
250 r	1	1	1	2	3	2	3	7	4	5	1	X	X	10
No primary reaction	1	..	1	..	1	5	5	3	..	..	8	..	8	8
Secondary erythema reaction (appearing nine to fourteen days after irradiation; all subjects tested showed this reaction within this period														
Minimum dose for secondary erythema reaction (number of cases for each dose)														
250 r	..	1	..	..	..	..	..	1	1	..	..	1	..	1
300 r	1	1	..	1	1	..	..	4	2	1	1	3	1	4
350 r	5	4	4	3	6	5	10	17	8	11	8	14	13	27
400 r	1	..	1	..	1	3	3	3	1	1	4	2	4	6
450 r	..	..	..	..	..	2	2	..	..	..	2	..	2	2
Pigmentation														
Number showing	5	4	5	2	8	10	13	21	8	11	15	15	19	34
Number not showing	2	2	..	2	..	..	2	4	4	2	..	5	1	6
Number of days before appearance of pigmentation (average for each group)	37	50	49	34	30	28	30	46	49	33	32	36	40	38
Disappearance of the reaction														
Average number of days after irradiation for each group	82	84	82	102	120	145	95	110	100	109	120	91	114	103

early reaction persisted and continued without subsiding into the secondary erythema. No special significance has thus far been attached to this phenomenon, other than the fact that such persistence does occur. Sometimes the primary reaction lasted only an hour, and if it did not persist and become blended with the secondary reaction it always subsided after ten hours.

Including the 60 subjects who could not be properly observed to obtain complete data, and hence are not included in the statistics of table 1, 100 subjects were irradiated. Of these, only 4 who showed a primary erythema required more than 350 r for the main, secondary reaction; so it appears to be almost axiomatic that if a primary reaction appears within a few hours the subject will require only 350 r or less for the real, secondary erythema. Perhaps additional study and further tests will further correlate these reactions and enhance the value of the primary reaction as an indicator of the probable sensitivity and tolerance of the subject's skin. The importance of this early reaction has been overlooked, and significant indications of possible cutaneous damage or intolerance can be obtained from it as well as from the later, secondary reaction. By thus avoiding the delay in waiting for the appearance of the secondary reaction, one of the principal obstacles which have discouraged dermatologists from making such tests would be removed, and the practice of pretherapeutic tests would be greatly facilitated.

The definition of the primary, or early, threshold erythema [8] reaction may be stated, from the statistics in table 1, as *the minimal amount of radiation which will produce within five to eleven hours after irradiation an erythema or pink reaction (whether mottled or homogeneous) with a sharply defined complete circular edge on an area 1 cm. in diameter on the upper, anterior, normally covered, portion of the thigh.* This is the same definition as for the secondary erythema, which is the only reaction which has usually been observed prior to this investigation, except for the specified time of appearance. The dose of unfiltered radiation, the technic factors for which have been previously described, which will produce the reaction defined as the threshold primary erythema is 250 r for 80 per cent of the subjects more than 10 years of age.

The minimum dose required to produce the threshold secondary reaction as defined in an earlier section of this paper was divided as follows among the 40 subjects tested: 250 r for 1 subject, 300 r for 4, 350 r for 27, 400 r for 6 and 450 r for 2. Three hundred and fifty roentgens was taken as the average threshold erythema dose, since 32 subjects

8. The primary and secondary reactions are herein defined in chronologic sequence; apparently the meaning has occasionally, elsewhere in the literature, been according to degree of importance, thus giving the reverse sense of the definitions used here.

(80 per cent) exhibited the reaction with 350 r or less. The required dose was less than 350 r in 5 cases (12.5 per cent). If the standard were taken as that dose producing a reaction in every case (100 per cent), the value would be 450 r, and the vast majority of the subjects (95 per cent) would exhibit greater than a threshold reaction, which would be of no value in the estimation of possible after-effects or for any other use, owing to the difficulty of judging the degree of the color reaction. If 350 r is chosen as the standard dose, it is the actual threshold reaction for 67.5 per cent (two thirds) of the subjects tested.

It is a coincidence that the percentage of subjects reacting to the dose chosen as standard (80 per cent) is the same as that selected by Dr. Quimby for her definition of the average threshold pigmentation dose.

The value of a cutoff point is well illustrated by the example cited, in which, if 450 r were chosen as the standard dose, 95 per cent of the subjects would exhibit greater than a threshold dose and the advantages of the threshold have been lost. The impossibility of judging degrees of reaction with any accuracy has been responsible for many of the discrepancies reported in the literature and for some of the misleading conclusions which have occasionally been drawn regarding the relative reactions with different qualities of radiation and similar questions. The essential point of the criterion proposed as a result of this work is the sharply defined, complete circular edge to the reaction, as limited by the aperture through which the exposure was made. This criterion enables all workers to record similar tests without objective variations in color perception or degree of reaction. A pink blush without a clearly demarcated edge was not regarded as a reaction in any of the tests recorded in table 1.

Brown pigment changes appeared in from fifteen to sixty days (average thirty-eight days) after the appearance of the secondary erythema reaction in 34 cases (85 per cent). Pressure with a glass slide was used to separate erythema and pigmentation reactions. In 6 cases the areas irradiated showed some pink coloration, without pigmentation, until they disappeared. The clinical signs of reaction to the radiation disappeared after thirty to one hundred and sixty days (average one hundred and three days). Miescher's third and fourth waves of reaction were rarely encountered, possibly owing to the fact that the radiation was softer (i. e., produced by a lower kilovoltage) than that used by him.

Coloring.—The subjects were divided into six different groups according to coloring of the skin and hair, and from the statistics in table 1 it is evident that there was no appreciable difference in the primary reaction information attributable to coloring with the exception of the group with dark and coarse skin. Only 50 per cent of the

subjects in this group exhibited the primary reaction, suggesting greater tolerance, or less sensitivity, of this type of skin. However, no foundation was observed for the oft repeated statement that fair complexions are more sensitive to the radiation. It has been a popular conception that an increase in pigmentation of the skin exerts a protective effect against roentgen rays, but there is no supporting proof of this to my knowledge. It appears that the greater difficulty in detecting pure erythema in more deeply pigmented skins may have given rise to this belief. One red-haired, fair subject and one light brunet showed no primary erythema at all.

All of the darker-skinned subjects showed pigmentation, and earlier than members of the other groups; the pigmentation persisted longer than the average, as well. No pigmentation was observed in 6 of the lighter-skinned subjects.

Sex.—There were no differences in the results in males and females which were conclusive and which could not be adequately explained on the basis of texture of the skin, the males, of course, having on the average coarser skins. Further investigation would be necessary to establish any difference attributable to the sex of the subject apart from coloring and texture of the skin, and certainly any such difference would be slight.

Age.—All subjects from 10 to 35 years of age showed the primary reaction, and the 2 exceptional subjects with light complexions who did not exhibit the primary reaction were in the group from 36 to 75 years of age. There appears to be a definite indication that older skins are less sensitive to the radiation, as evidenced both by the primary and by the secondary erythema reactions.

The range of the period of duration of the primary reaction is shorter and the average duration is decidedly less for the older group. Six subjects in the group 36 to 75 years of age required 400 to 450 r for the secondary erythema reaction. All the older subjects showed pigmentation which on the average lasted longer, although in several older subjects the reaction disappeared comparatively early. There seemed to be little difference between the groups from 10 to 18 years and from 19 to 35, although there was a tendency for the younger group to have more members who showed the secondary erythema with less than 350 r.

Texture of the Skin.—The analysis with respect to texture of the skin seemed to be the most enlightening of all. The persons with coarse, greasy skins appear to be the most tolerant group, as a whole. All 8 subjects who did not show the primary reaction were in this group; fewer of the subjects in this group showed persistence of the primary reaction merging into the secondary; the 6 elderly patients who

required 400 to 450 r for the secondary erythema reaction also had this coarse greasy type of skin, so that this aspect cannot be solely assigned either to age or to texture of the skin. The reaction tended to last longer than average for this group. Five of the subjects with fine skin but only 1 with coarse skin showed no pigmentation.

Summary of Indications from Adult Erythema Tests.—In all cases observations were made six hours after irradiation and then every two days until sixteen days had elapsed, and from then until all clinical signs had vanished examinations were made twice weekly.

As previously stated, 60 other subjects were tested, and although they were not examined regularly, and hence were not included in table 1, in general they substantiated the indications shown.

From the tests on subjects from 10 to 75 years of age, the following indications are evident:

1. Persons with fair skins of fine texture tend to exhibit visible primary and secondary erythema reactions more frequently and with smaller doses, in general, than those in the other groups.

2. There are exceptions even in this group, and persons may be encountered who require more than 350 r for the secondary reaction and who do not have the primary reaction at all.

3. Conversely, exceptions may occur in persons with dark, coarse skin, and both primary and secondary reactions may appear with lower doses. Complexion cannot be regarded as a reliable guide to possible roentgen ray sensitivity.

4. These observations demonstrate clearly that ionization measurements alone are not sufficient for many dermatologic treatments over large areas or for long periods, as in the treatment of acne.

5. The primary erythema reaction, previously not noted to be of any special significance, from the data in table 1 and from other experiments, appears to be of almost as much significance as the secondary erythema reaction. It shows up in from five to eleven hours (average seven and four-tenths hours) in cases in which the secondary threshold erythema reaction is produced by 350 r or less and is produced itself by from 200 to 250 r. An occasional exception may occur, probably due to one of the following reasons: (*a*) variation in general health of the subject, (*b*) amount of blood present in the irradiated area and condition of circulation, (*c*) previous exertion, (*d*) individual variation in reactivity of the skin and (*e*) experimental error.

6. The extremely close relation between the primary and the secondary reaction is of significance only in the range of dosage up to 450 or perhaps 500 r. Above that level both reactions occur almost invariably and merge into one another; furthermore, the secondary reaction becomes proportionately greater as the dosage increases.

7. The factors which have most influence on the reactivity of the skin are, in order of their importance: (*a*) age, (*b*) texture of the skin and (*c*) complexion. With respect to age, the group of subjects from 36 to 75 years of age required greater doses to produce the secondary erythema reaction, and the majority showed no primary erythema reaction. Coarseness and greasiness of the skin appeared to cause greater tolerance, because of greater thickness of the epidermis or for some other reason. Complexion alone did not seem to be an accurate guide to tolerance, but when it was combined with texture the results were consistent: five of 10 persons with dark, coarse skins exhibited the primary reaction, and the same 5 required only 350 r for the secondary erythema, the other 5 subjects requiring 400 to 450 r.

8. Thickness of the skin seems to be a factor of some importance in relation to tolerance of roentgen radiation. When subjects exhibited unexpected apparent tolerance, the coarse greasy type of skin was usually found to be present. Also in my experience telangiectases are more easily produced on *covered* areas of the body, such as the upper part of the trunk, when larger doses of roentgen rays (as in the treatment of basal cell epitheliomas) are given, than on *exposed* areas, like the face and neck. This again suggests greater tolerance and may be due to a thickening of the epidermis in the latter areas, possibly assisted by exposure to the sun and weather, which may also lessen the sensitivity to roentgen radiation. A few subjects were tested in the axillas, elbow flexures and groins, and these areas were found to exhibit a more noticeable erythema reaction for similar doses than did nonflexural areas. This may be due to a relative lack of thickness of the epidermal structure in the flexures, as a comparatively wide variation in thickness of the skin on different areas of the body has been shown to exist by Maximow and Bloom.[9] The thickness was found by them to vary, in so far as the epidermis is concerned, from an average of 0.07 to 0.12 mm. on the body and limbs to an average of 0.8 to 1.4 mm. on the palms and soles. They observed that the cutis varied in thickness from an average of 1 to 2 mm. on the body and limbs, 0.6 mm. on the eyelids and prepuce and up to 3 mm. on the palms and soles.

9. In half the cases in which the primary erythema reaction occurs, it continues as such and merges into the secondary reaction.

10. Miescher's third and fourth waves in the pigmentation stage are not consistently observed at kilovoltages around 110.

11. Changes in the pigment occur earlier, as a rule, in persons with dark complexions and last relatively longer.

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9. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 3, Philadelphia, W. B. Saunders Company, 1938, p. 325.

12. Erythema reactions tend to be more visible in persons with fair skin, not through greater sensitivity to radiation but through lack of pigment and outer protective covering which tend to mask the dilatation of the capillary blood vessels in the skin.

SUMMARY OF ERYTHEMA TESTS ON INFANTS FROM THREE WEEKS TO SIX MONTHS OF AGE

Shortly after the completion of the adult erythema tests, the x-ray tube which was used burned out. It was replaced by a General Electric, shock-proof, oil-immersed, water-cooled tube with an inherent filtration of approximately 1 mm. of aluminum. The technic factors with this new tube were: 100 kilovolts, 6 milliamperes, 20 cm. target-skin distance, mechanical rectification, 195 r per minute, in air, and a half value layer of 1.7 mm. of aluminum. With this technic similar tests were performed on infants, since they could be held in position without risk of shock to assistant or subject, owing to the fact that the equipment was shock proof.

Table 2 gives the statistics for these experiments, which were performed on 22 subjects. Only 1 subject failed to show a primary erythema reaction, and this was a red-haired infant with a pink complexion. The test was repeated a second time with the same result. The fact that 21 of the 22 subjects showed the primary reaction regardless of coloring (which varied little among the infants tested, except for color of hair) agrees with the experiments on adults in demonstrating the greater apparent radiosensitivity of younger subjects.

The time of appearance of the primary reaction varied from three to eight hours (average, five hours), which is decidedly less than that obtained among the adult subjects; it appeared earlier, on the average, in females than in males. In all cases in which the primary erythema reaction occurred at all, it persisted without subsiding into the secondary erythema, which suggests greater apparent radiosensitivity or less power of recovery, or both, than in adults for this particular phase of the reaction.

The minimum dose required to produce the primary reaction varied from 200 to 350 r (a wider range than among adults); if 50 r is subtracted owing to the greater inherent filtration of this new tube, as indicated by the tests on adults with various filtrations, the range becomes 150 to 300 r. The explanation for this wide range appears to be obscure, but apparently it indicates a more varied range of radiosensitivity among infants, at least as far as the primary reaction of the threshold erythema test is concerned.

The secondary erythema reaction was produced by 250 r in 2 subjects, 300 r in 7 subjects and 350 r in 12 subjects, and 500 r was required for the red-haired male infant who did not show the primary reaction in two separate tests. If allowance is made for the greater inherent

filtration of the new tube, and 50 r is subtracted in each case, 95.5 per cent of the subjects showed the secondary reaction with 300 r or less. This also indicates a greater apparent sensitivity or reactivity among infants than among the adults in the secondary phase as well.

TABLE 2.—*Results of Threshold Erythema Tests in Infants*

	Coloring				Sex		
	Red Hair and Fair Complexion	Fair Hair and Fair Complexion	Medium	Dark	Male	Female	Totals
Total number of cases in each group	2	8	8	4	8	14	22
Primary erythema reaction (appearing three to eight hours after irradiation)							
Showed reaction							
Number	1	8	8	4	7	14	21
Per cent of total group	50	100	100	100	88	100	95
No primary erythema							
Number	1	0	0	0	1	0	1
Per cent of total group	50	0	0	0	12	0	5
Time of appearance (hr.)							
Range	5	3 to 7	4 to 7	4 to 8	4 to 8	3 to 7	3 to 8
Average	5	4.75	5.5	6	6.2	4	5
Period of duration (hr.) *							
Cases in which primary reaction persisted into secondary erythema without subsiding							
Number	1	8	8	4	7	14	21
Per cent of cases which showed primary reaction	100	100	100	100	100	100	100
Minimum dose for primary erythema (number of cases for each dose)							
200 r	..	..	4	..	..	4	4
250 r	..	4	2	..	3	3	6
300 r	..	4	2	2	4	4	8
350 r	1	..	..	2	..	3	3
No reaction	1	..	..	..	1	..	1
Secondary erythema reaction (appearing nine to fourteen days after irradiation; all subjects tested showed this reaction within this period)							
Minimum dose for secondary erythema reaction (number of cases for each dose)							
250 r	..	2	..	..	..	2	2
300 r	..	3	4	..	3	4	7
350 r	1	3	4	4	4	8	12
500 r	1	..	..	..	1	..	1
Pigmentation (appearing in an average of twenty-five days after irradiation)							
Number showing	..	6	6	3	7	8	15
Number not showing	2	2	2	1	1	6	7
Disappearance of the reaction							
Average number of days after irradiation for each group	25	43	56	50	45	48	47

* In all cases in which the primary reaction occurred it persisted into the secondary reaction.

The tendency was noticeable for the fair-haired, fair-skinned infants to be more radiosensitive and also for females to be more sensitive than males, as was found in the adult series, within the limits of experimental error. Brown pigment changes occurred in a smaller proportion

of infants than adults and appeared, on an average, within twenty-five days in 15 subjects. This was considerably earlier than the average time among adults. The tendency for pigment changes to occur was greater in males than in females.

The reaction disappeared noticeably earlier (average, forty-seven days) than in adults, which suggests a greater recuperative power in younger tissues. Consequently, it seems not unreasonable to suppose that young tissues will tolerate roentgen rays at least better than was previously supposed. It has been an accepted belief for some time that immature, abnormal or pathologic tissue cells are more susceptible to damage by roentgen rays than are normal cells. This belief has also been extended to young tissue cells, such as those found in infants. I am somewhat inclined to doubt the latter belief, provided that the cells themselves are mature (in so far as they are perfectly formed, as contrasted with immature embryo cells) even if the subject is immature with respect to actual age. It seems feasible that an infant would exhibit a more intense degree of reactivity on account of its youth, but that this is counterbalanced, at least partially, by its greater recuperative ability. This greater reactivity and recuperative power of a younger subject would also explain why therapeutic results with roentgen rays can be obtained with smaller doses in a child than in an adult, as, for example, in the treatment of plantar warts. The greater apparent reactivity of the tissues of a young person and the aforementioned belief concerning the susceptibility of immature cells to roentgen rays may have given rise to the impression that young tissues, even though fully formed, were more easily damaged than is actually the case. Their greater proportionate recuperative ability, as represented by the earlier disappearance of all signs of the threshold erythema tests, suggests that larger doses of roentgen rays can be given to young subjects without after-effects than has previously been the belief. I have found this to be true clinically in the treatment of vascular nevi with roentgen rays, also.

All tests on infants were performed on the flexor surface of the forearm, since the wetting of napkins was found to influence materially the results of tests on the thighs. The difference in the part of the body irradiated would account to a slight degree for the tendency toward greater sensitivity than in adults but not to a degree sufficient to influence the comparison. The same six apertures were employed for the tests on infants as were used for adults.

FURTHER OBSERVATIONS AND ADDITIONAL TESTS MADE ON ADULTS

EXPERIMENT 1.—A sheet of ordinary lint was placed under three of the six apertures in the tin and lead alloy foil shield, and all were exposed to the average threshold erythema dose on the usual area of the thigh.

The primary and secondary reactions were similar over all six areas. This supports the contention that the primary reaction is a real roentgen ray effect and is not due to ultraviolet radiation, as some observers formerly supposed. The same results were obtained with a layer of ordinary adhesive tape placed over three of the six apertures. Goldsmith,[10] as previously discussed,[1] noticed the "early," or primary, erythema reaction, and, to eliminate the possibility of its being due to other than the effect of the roentgen rays, he covered the field and surrounding area with white lint; this did not prevent the early erythema reaction.

EXPERIMENT 2.—Several apertures, each 1 cm. in diameter, were punched in a piece of the alloy foil, and the device was then fastened to the usual upper aspect of the thigh. Five-tenths to 1 mm. of foil separated each aperture from the neighboring ones. All areas were exposed simultaneously to a threshold erythema dose of roentgen rays on 5 subjects, and the same areas on 5 others were exposed to a dose of 600 r. The primary and secondary reactions were clearly demarcated in every case and never encroached on the narrow intervening protected strip of skin. This observation rules out the possibility of the liberation of histamine, or of the H substance (of Lewis), being the cause of the dilatation of blood vessels; otherwise the areas of erythema would have spread peripherally and overlapped the intervening strips of shielded skin.

The primary erythema reaction may possibly be due to very soft secondary roentgen rays characteristic of the atoms composing the irradiated tissue. This type of radiation would be very soft (of comparatively long wavelength in the roentgen ray range), and its effect might parallel that of ultraviolet radiation, which produces an erythema within a few hours by action on the superficial capillary blood vessels. The real secondary erythema, on the other hand, may be due to the much shorter wavelengths composing the bulk of the beam of rays from the x-ray tube. The comparative effects here postulated correspond to the observed behavior of various qualities of radiation in the direct beam, the softer radiations being more readily absorbed in the skin and producing an erythema reaction with smaller doses than are required with the harder radiations. If the primary erythema corresponds to an ultraviolet ray type of reaction and is produced by secondary radiation characteristic of, or scattered by, the atoms of the tissue, there is no problem of transmission of this relatively nonpenetrating type of radiation, since it is produced right at the structures involved in the reaction.

EXPERIMENT 3.—It was noticed that during the tests on some days areas which received a smaller dose were darker (in shade of reaction)

10. Goldsmith, W. N.: Some Notes on the Biological Determination of the Erythema Dose of X-Rays in r-Units, Brit. J. Dermat. **51**:126, 1939.

than other areas which received a greater dose. This was difficult to explain with any degree of certainty and was noticeable in only a small proportion of the cases. The variation in tint, however, did not affect the clearly demarcated complete circular edge, which was the criterion for the threshold erythema reaction. Furthermore, if the two parallel rows of three apertures each, in figure 1, were placed too far apart, the row nearest the outer aspect of the thigh tended to react less than the row nearest the inner aspect, for equal doses. For this reason the two rows were placed as close together as possible, so that they were both on an almost flat surface; this helped eliminate the possibility of the natural curve of the thigh causing an appreciable difference in the distance from the target of the x-ray tube and also eliminated any effect due to the greater apparent sensitivity of the inner aspect of the thigh relative to the outer aspect.

Time of Appearance of Primary Reaction.—The time of appearance of the primary reaction sometimes differed noticeably in the same subject, possibly owing to the state of the circulation and health of the person at the time of irradiation or examination or even to the amount of movement or exertion immediately prior to irradiation or examination. The latter may influence the dilatation or dilatability of the cutaneous blood vessels, thus affecting the amount of blood present in the tested area. An increased blood supply tends to accentuate the threshold erythema reaction.

Minimum Epilation Dose.—Some observers claim that the minimum epilation dose of roentgen rays is the best biologic test of sensitivity. On the other hand, I have found that at 60 kilovolts, 4 milliamperes and 20 cm. target-skin distance, without filtration, the secondary erythema dose corresponds approximately with the epilation dose. As the kilovoltage is increased, the erythema reaction requires more roentgens for its production, while the number of roentgens required for epilation increases little, if at all in the same subject, up to 130 kilovolts and with filtrations up to 3 mm. of aluminum. Above that range I cannot speak from personal experience. The epilation is probably an effect on the hair follicles, or even on the papillae themselves, rather than on the blood vessels supplying them. This is also suggested by the fact that complete epilation of the scalp can be produced by roentgen rays, followed by regrowth of the hair; whereas when thallium acetate is used, a fringe of hair is left on the forehead, and the median parts of the eyebrows and the eyelashes are also unaffected. These areas are not supplied by sympathetic trophic nerves, which are apparently the mediums through which thallium acts in the production of epilation of the scalp. It is evident that the hair follicles or papillae of the scalp (if they are the affected part when the hair falls) are particularly susceptible to roentgen rays, because epilation can be produced on a

closely shaved scalp without the production of an erythema reaction. A greater dose than a threshold erythema dose is usually necessary to produce epilation of the body hair; consequently, epilation of hair of the scalp or body does not give an indication as to possible future damage to the skin generally, whereas threshold erythema tests apparently do give such an indication. It must be admitted that the threshold erythema test may not be an exact criterion of the action of roentgen rays on all epithelial or other body cells; but it is the only clinical and biologic test which is available at present, and it gives more general information than does hair epilation, which is apparently less affected by changes in the quality of the radiation than are the blood vessels of the skin. Furthermore, erythema tests may be performed on covered surfaces of the body without the production of a bald patch on the scalp, which is a source of embarrassment for most patients. The epilation dose test is not to be recommended for pretherapeutic testing purposes or for the so-called biologic standardization of the x-ray equipment.

Maximum Tolerated Dose.—Other authorities prefer the maximum tolerated dose for the tests, which is, on an average, approximately double the minimum epilation dose. It would seem unwise to apply this test as a routine, owing to the variation in sensitivity in some persons; a certain percentage of the patients tested would of necessity receive greater than their individual tolerated dose in order to arrive at an average value, with resulting cutaneous sequelae in these instances. Although some authorities hold the view that there is no difference in the susceptibility of the skin of different persons to roentgen rays, I do not believe this to be true, even though I am of the opinion that the generalization that fair-skinned persons are as a rule more susceptible than dark-skinned persons is not true either. Not only do the experimental tests in this research program show a definite variation in the degree of erythema for some subjects (for instance, the red-haired, fair-skinned infant who required 400 r for the production of the threshold erythema reaction), but also my own clinical experience has demonstrated over and over again variations in individual susceptibility or sensitivity to roentgen rays in a small percentage of cases. For example, there is the occasional patient suffering from acne, who exhibits an exacerbation of symptoms after the first or second dose of roentgen rays (100 r), and also there is the occasional patient who shows a faint erythema reaction after 150 r. The latter reaction has been encountered by numerous dermatologists with whom I have discussed it. Again, there is the occasional patient in whom a basal cell epithelioma is given an ordinary lethal dose of roentgen rays (varying from 1,400 to 2,000 r) at one sitting over a circular area not exceeding 4 cm. in diameter, and the treatment is followed by a radionecrosis for no observable reason, despite accurate measurement and delivery of the dose. Numerous

authorities with whom I have communicated, such as Drs. MacKee, Andrews and Quimby, have all noted and recognized individual susceptibility to roentgen radiation; numerous references may be found in the literature in support of this contention, and those therapeutists not agreeing possibly do not give sufficiently large doses for the phenomenon to be evident.

Individual Cutaneous Sensitivity.—It is well known that there is a definite variation in individual cutaneous sensitivity to various forms of external irritants, such as chemicals, soaps and other substances with which the skin comes in contact in various occupations. Why, therefore, should roentgen rays be the exception and not pick out similar variations in individual cutaneous sensitivity? I feel confident that they do, and that so-called "apparent" differences in sensitivity cannot all be accounted for by experimental error. Therefore, it would seem far wiser to estimate the maximum tolerated dose than to employ it as a test dose; it cannot be as valuable as the threshold erythema dose in routine estimations of individual cutaneous sensitivity, and if it is exceeded in any patient, by definition that patient would suffer from damage to the skin and serious sequelae.

EXPERIMENT 4.—*Recovery.*—On 10 subjects, five circular areas, each 2.5 cm. in diameter, were exposed on the upper anterior aspect of the thigh. The technic factors were the same as for the tests on infants, namely: 100 kilovolts, 6 milliamperes, 20 cm. target-skin distance and 195 r per minute, in air, with a half value layer of 1.7 mm. of aluminum. Four hundred roentgens was administered to one area, and 200, 250, 300 and 350 r to the other areas; the latter areas were also irradiated after twenty-four hours. These areas were observed again in seven days and daily thereafter for another seven days. The secondary erythema appearance was determined in an endeavor to estimate skin-tissue recovery during the twenty-four hours between irradiations, as performed by MacComb and Quimby [11] with their pigmentation tests. The average threshold erythema dose, with the new tube operating as previously described, was 400 r when given at one sitting (being higher than that reported in the data in table 1 owing to the fact that the radiation was harder: a half value layer of 1.7 mm. of aluminum instead of 0.9 mm.). For two doses at twenty-four hour intervals a total of 520 r (260 r each) was required. This total was 130 per cent of that required when given at a single sitting. The percentage of recovery in the twenty-four interval was 46, and the amount "remaining" of the first day's dose, to be added to the second day's dose of 260 r, in order

11. MacComb, W. S., and Quimby, E. H.: The Rate of Recovery of the Human Skin from the Effects of Hard or Soft Roentgen Rays or Gamma Rays, Radiology **27**:201, 1936.

to give the same effect as 400 r given at once on the second day, was 140 r, or 54 per cent of the dose given on the first day. MacComb and Quimby found 152 per cent was required if administered on two days as described, there being 69 per cent recovery and 31 per cent remaining of the first day's dose on the second day. Their experiments were performed with roentgen rays at 200 kilovolts applied to an area of 10 by 10 cm., however.

Reisner [12] in similar experiments with roentgen rays at 200 kilovolts and fields 2 by 2 cm. used a sharp erythema reaction as a criterion, and his observations showed 46 per cent recovery in twenty-four hours, with

TABLE 3.—*Recovery of Skin Following Roentgen Irradiation*

	Belisario	MacComb and Quimby [11]	Reisner [12]
Kilovoltage of roentgen rays used	100	200	200
Criterion of reaction used	Threshold erythema dose	Threshold pigmentation dose	Sharp erythema reaction
Standard single dose given at a single sitting	400 r	525 r	1,000 r
Interval between the two divided doses	24 hours	24 hours	24 hours
Dose in roentgens for each day of the divided dose	260 r	400 r	650 r
Total of the divided dose (two days)	520 r	800 r	1,300 r
Percentage of standard single dose corresponding to total divided dose	130	152	130
Standard single dose minus second day's divided dose = amount remaining from first day's divided dose	140 r	125 r	350 r
Percentage of first day's dose corresponding to amount remaining (shown in line above)	54	31	54
First day's divided dose minus amount remaining = amount of recovery (%)	Recovery in 24 hr.: 46%	Recovery in 24 hr.: 69%	Recovery in 24 hr.: 46%

54 per cent remaining, and the total divided dose was 1,300 r, or 130 per cent of the standard single dose of 1,000 r, values identical with mine. However, since accuracy in determining the actual tint of the reaction is much more difficult than in determining a threshold erythema, it is possible that his figures might differ somewhat if the latter criterion were used, because of the difference in the quality of the radiation.

Although only 10 cases were included in my series, the close degree with which the findings correspond to Reisner's, who also used an erythema criterion (although not a threshold), may indicate a considerably lesser degree of recovery of the skin when an erythema is evoked than when the pigmentation criterion is used according to the method of MacComb and Quimby. These observations are summarized in table 3.

12. Reisner, A.: Hauterythem und Röntgenstrahlung, Ergebn. d. med. Strahlenforsch. **6**:1, 1933.

EXPERIMENT 5.—*Back Scatter and Tissue Injury.*—On another 10 subjects the same technic factors and the same region of the thigh were used for a test with different-sized fields. Four hundred roentgens (the average threshold erythema dose with a half value layer of 1.7 mm. of aluminum) was delivered to a circular area 1 cm. in diameter. Various fractions of this dose were delivered to three other circular areas 2.5 cm. in diameter and to three areas 5 cm. in diameter; the areas of these apertures were, respectively, approximately 0.8, 4.9 and 19.6 sq. cm. They were arranged as shown in figure 3.

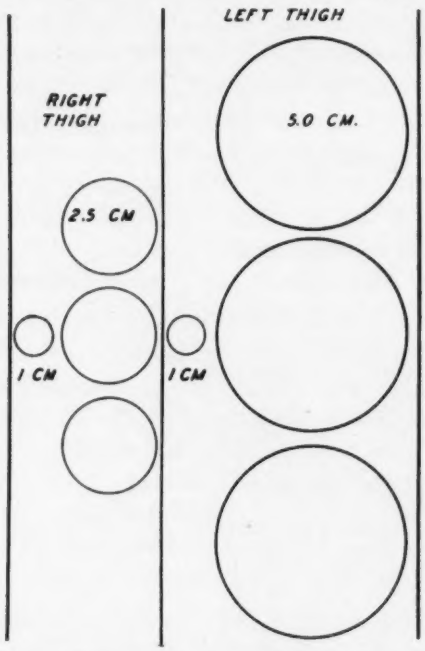

Fig. 3.—Arrangement of apertures for tests of the effect of field size on erythema dose reaction (one-half actual size).

Since the back scatter for an area 1 cm. in diameter is negligible, the extra amount of radiation due to back scatter for the other areas is actually the full amount of back scatter for those areas; according to Quimby, Marinelli and Farrow,[2] these amounts would be 12 per cent for the circle 2.5 cm. in diameter and 18 per cent for the circle 5 cm. in diameter. The amount by which the back scatter of the 5 cm. circle exceeds that of the 2.5 cm. circle is therefore approximately 6 per cent. Similar threshold erythema reactions were obtained for the larger areas with 16 per cent less radiation for the field 2.5 cm. in diameter than for the standard field 1 cm. in diameter and 33 per cent less for the 5 cm. field than for the 1 cm. field. This amounts to a difference of 17

per cent in the dose required for the 2.5 and 5 cm. areas. Four per cent of the difference between the 1 and the 2.5 cm. field cannot be accounted for by back scatter, and 11 per cent of the difference between the 2.5 and the 5 cm. field cannot be accounted for by back scatter; similarly, 15 per cent of the observed 33 per cent difference between the 1 and the 5 cm. area must be due to something other than back scatter. This difference must be ascribed to volume or tissue injury effect.

These observations were compared with those made after the application of solid carbon dioxide to 6 subjects. This was applied for ten seconds to an area of skin 1 cm. in diameter and for varying shorter periods to areas 2.5 and 5 cm. in diameter. The results of these tests closely approximated the tissue injury effect with roentgen rays. The

TABLE 4.—*Back Scatter and Tissue Injury*

	Compared with Field * 1 Cm. in Diameter		Compared with Field 2.5 Cm. in Diameter
	2.5 Cm. in Diameter (5 Sq. Cm.)	5 Cm. in Diameter (20 Sq. Cm.)	5 Cm. in Diameter (20 Sq. Cm.)
Per cent by which back scatter alone increases the effect of a given dose (Quimby [2])	12% (due to back scatter only)	18% (due to back scatter only)	6% (difference in back scatter)
Actual clinical determination of the effect of field size (per cent by which dose must be decreased for larger field in order to get equal clinical effect on the skin)	16% (total clinical effect)	33% (total clinical effect)	17% (difference in total clinical effect)
The difference between the first two items is the amount of increase in the effect observed which is not due to back scatter, which equals the per cent of increase in reaction for larger fields due to tissue injury	4% Tissue injury	15% Tissue injury	11% Greater tissue injury for the larger field

* Back scatter is considered negligible for a field 1 cm. in diameter (0.8 sq. cm.).

volume involved increased with the surface area of skin exposed, of course. The decrease in time of application necessary to produce in the larger areas a similar bulla, having also the same appearance when healed, as that produced by the ten seconds' exposure on the 1 cm. diameter field, which was chosen as the standard of comparison, was very nearly the same as the decrease in dose for equal roentgen ray erythema effects; the actual percentage values were the same within the margin of experimental error. The use of solid carbon dioxide as a comparative test was suggested from the fact that in the treatment of vascular nevi I had noticed frequently that a ten second application of the substance to a small area would produce a superficial bulla which healed quickly without scar formation, whereas in a larger area the same application was usually followed by a slough and superficial scarring. Figure 3 shows the arrangement of areas used in the back scatter and tissue injury experiments, and the results are recorded in table 4.

These experiments indicate that back scatter is not the only factor to be taken into consideration in estimating doses of roentgen rays for large areas; there is a definite tissue injury effect which should be taken into consideration. This tissue injury effect can be produced by any form of injury to tissues apparently, whether it be mechanical, chemical, thermal or by radiation energy. It is distinct from back scatter, which is peculiar to roentgen rays, and has received little attention in the estimation of possible tissue damage when roentgen rays are administered over large areas of skin, thereby affecting a large volume of tissue owing to the appreciable depth penetration of the radiation. It would seem from these experiments that cutaneous tests are of more value for superficial than for deep roentgen therapy, because when large areas are irradiated with higher voltages the tissue injury effect becomes more pronounced, not only on the surface but also in the volume of tissue affected below the surface. A further argument for cutaneous tests prior to roentgen ray therapy on the skin, even in cases of epithelioma, is that, being more accessible, such lesions may often be eradicated with some thought of the cosmetic result if attention is paid to the size of the area involved and to the tolerance of the subject. Ionization measurements and calculations of the back scatter fail to give complete information with regard to later tissue injury to a greater and greater degree as the size of the field and the penetration of the radiation increase. Such a discrepancy can be overcome only by further investigations of the part played by the tissue injury factor.

EXPERIMENT 6.—*Rate of Administration.*—Five subjects were given radiation in two areas, each 2.5 cm. in diameter, on the same upper anterior aspect of the thigh, with the following factors: 60 kilovolts, 20 cm. target-skin distance, 8 milliamperes and 150 r per minute. Four hundred roentgens were given under these conditions to one of the areas. The same dose was then given to the other area, using 2 milliamperes and 27 r per minute. The same quality (inherent filtration of approximately 1 mm. of aluminum) was used for all ten exposures. No difference was noted in the primary or secondary erythema reactions with the two different intensities, indicating that within this range of rate of administration intensity apparently exerts no noticeable effect on the clinical appearance of the reaction.

EXPERIMENT 7.—*Roentgen Rays Combined with Infra-Red and with Ultraviolet Rays.*—Five subjects were given 400 r with 100 kilovolts, 6 milliamperes, 20 cm. target-skin distance, 195 r per minute and a half value layer of 1.7 mm. of aluminum, on the same region of the thigh, in three circular areas, each 2.5 cm. in diameter, arranged longitudinally and with the margins separated by 2 cm. from one another. On one of the three areas roentgen rays alone were given; on a second an

erythema dose of ultraviolet radiation (quartz mercury vapor lamp for six minutes at 17 inches [43 cm.]) was given immediately prior to the roentgen ray irradiation. On the third area infra-red rays were given for fifteen minutes immediately prior to the roentgen ray irradiation, so that a bright pink flush was evident when this area was exposed to the roentgen rays. The infra-red rays consisted of combined emittent and nonemittent rays at a distance of 12 inches (30 cm.).

The subjects were examined two hours after irradiation, and in every case it was noted that the area which had received the infra-red prior to the roentgen rays was showing a pink reaction with a sharply demarcated outline and that there was no reaction in either of the other two areas. Four hours later, when the ultraviolet reaction was well established, the area which had received the ultraviolet irradiation appeared darkest, as the erythema due to the infra-red rays had by that time subsided. The area which had received the roentgen rays only was always the faintest of the three, whether it was at the top, center or bottom of the row. The following day the area which had received the infra-red rays was much brighter than that which had received ultraviolet rays, and the latter area was in turn darker than the area which had received roentgen rays only. The subjects were observed every two days, and right through into the secondary reaction the infra-red area was markedly brighter than the area which had received ultraviolet rays. When the secondary erythema appeared the area which had received roentgen rays alone was still the faintest of the three. The areas which had received infra-red did not show pigmentation, and the reaction had disappeared in an average of eleven weeks. The areas which had received ultraviolet rays, however, showed pigmentation early, and the reaction lasted the longest of those in the three areas (an average of sixteen weeks).

The indications from this small series of tests suggest that an increased blood supply present in an irradiated area increases the action of the roentgen rays on the blood vessels or on whatever tissue it is on which they exert their effect to produce dilatation of the blood vessels. It has been suggested that when the blood supply to an area of the body is increased, there is an increased amount of iron present in the hemoglobin which increases the secondary radiation locally at the vessel, thus increasing the reaction. This suggestion, however, is conjectural and is not founded on any definite evidence. A further observation tending to indicate some action relative to the vessels themselves is that infra-red rays tend to diminish (or, at least not increase) pigment formation whereas ultraviolet rays, which alone cause pigmentation, in conjunction with roentgen rays tend to increase pigmentation.

The most important indication appears to be that infra-red rays delivered immediately prior to roentgen rays increase the action of the

roentgen rays. This suggests the possibility of employing infra-red irradiation prior to roentgen ray irradiation on an area where circulation is bad (i. e., over cartilage or on the back of the hand) or where much previous roentgen ray exposure has been given. In such cases, an application of infra-red rays might allow a smaller dose of roentgen rays to be given and still produce the required therapeutic result. This would lessen the risk of later tissue damage but would still produce the required therapeutic effect. Further investigation is necessary, however, to verify or disprove this possibility.

SUMMARY AND CONCLUSIONS

A new criterion of reaction is proposed resulting in the formulation of an easily recognized and readily reproducible standard threshold erythema dose.

The size chosen for the irradiated area was 1 cm. in diameter, since in the first paper [1] of this series it was shown that the size of the fields employed in practice vary widely and that the back scatter and tissue injury factors contribute to the discrepancy in erythema dose values in use.

Erythema reactions are believed to be superior to other standard dose tests as indicators of possible future damage to the skin.

In a review of the literature [1] the value of the cut-off end point afforded by a threshold reaction was demonstrated; this was further demonstrated in the results of the tests herein reported.

The value of the primary, or early, erythema reaction, which has been previously neglected, as an indicator of future damage to the skin is described.

The effect of different qualities (filtrations) of radiation was investigated, and the required dose was found to increase with increasing hardness of the radiation.

The average threshold erythema dose (in 80 per cent of the subjects) for a half value layer of 0.9 mm. of aluminum was found to be 350 r for a field 1 cm. in diameter.

The results of the erythema tests were analyzed according to coloring, sex, age and texture of the skin.

A series of tests was made on infants, and the definite data obtained contradict many previously accepted theories.

The following special subjects were discussed and separate series of tests were conducted to investigate many of them:

(*a*) nature of the primary erythema reaction, (*b*) eliminating liberation of histamine as a causative agent, (*c*) variation in tint in the same person, (*d*) variation in time of appearance in the same person, (*e*) relation to epilation and individual idiosyncrasy, (*f*) rate of recovery, (*g*)

back scatter and tissue injury, (*h*) effect of rate of administration and (*i*) roentgen rays combined with infra-red and with ultraviolet rays.

The importance of tissue injury as a factor to be considered in addition to back scatter for larger fields is stressed.

Since with modern instruments of measurement the dose can be determined exactly, and since it varies with each installation, a more exact determination of exposure than a convenient integral number of minutes corresponding approximately to a fraction of the erythema dose is possible. A change in technic of successful treatment is not advocated, but the expression of these successful doses as different fractions of a standard erythema dose rather than the same fraction of different standard doses would be more enlightening and should facilitate the advancement of the art of therapy.

NOTE.—The author was unable to pursue these studies and experiments further owing to the outbreak of war, for he was accepted for active service and is abroad at present with the Australian Imperial Force. Correspondence will be handled or referred by Mr. Robert E. Pugh Jr., 344 Malcolm Drive, Pasadena, Calif.

COMMON FUNGOUS INFECTIONS OF THE FEET AND GROINS

NEGLIGIBLE ROLE OF EXPOSURE IN CAUSING ATTACKS

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Many years of observation on a considerable amount of clinical material have convinced us that exogenous infection (i. e., exposure to other patients in active phases of the disease) has played no role in the production of attacks of ringworm of the feet and groins in our patients. On the contrary, almost all of our adult patients can at all times be shown to carry the pathogenic fungi in quiescent foci on the feet, toe nails or groins, but they have exacerbations of common forms of "ringworm" only when certain contributory or trigger factors lower their resistance to their own germs. We now, therefore, tell our patients with the common forms of fungous infections of the groins and feet that the disease is rarely, if ever, "contagious" for other members of the family or household, and we abstain from giving directions for the protection of others and confine our efforts to the treatment of the infected person and to the institution of simple prophylactic measures designed to prevent recurrences in the patient himself.[1]

The results of this approach have been eminently satisfactory, for we can record no case of familial or conjugal transmission of ringworm in our material during the last ten years. Our opinion and experience on this subject correspond to those of certain of our colleagues but

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Read by title in a symposium on Superficial Fungous Infections at the Sixty-Fourth Annual Meeting of the American Dermatological Association, Inc., New Orleans, April 10, 1941. The other papers in the symposium have already been published (Arch. Dermat. & Syph. **44**:800-840 [Nov.] 1941).

1. Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1937, p. 20. Sulzberger, M. B., and Wolf, J.: Dermatologic Therapy in General Practice, ibid., 1940, pp. 276-280.

diametrically contradict the opinions held, expressed and published by many others regarding the extreme "contagiousness" of this form of ringworm.

This difference of opinion is not a purely academic matter. If the attacks of ringworm of the feet and groins are really regularly produced by new exposures to fungi, then the prophylactic and fungicidal procedures being exercised by millions of people in millions of homes, clubs and institutions are warranted. If, however, as our experience indicates, not exposure to new germs but variation in degree of "host resistance" is the determining factor in the production of clinical activity, then the often difficult, disagreeable, expensive and potentially skin-damaging prophylactic measures being employed and recommended are to the greatest degree unnecessary.[2]

The question appears to us to be of great general importance, for the fungous infections here under consideration are among the most common of human diseases.[3] And there is at this particular time an additional need for accurate knowledge concerning possible modes of transmission and the causation of attacks, for ringworm of the feet and groins accounts for a significant proportion of all military disability. We therefore felt that it would be valuable to assemble and analyze on a statistical basis the opinions and experiences of a group of outstanding dermatologists who during the last twenty or more years have observed, studied and treated a sum total probably aggregating hundreds of thousands of patients with fungous infections of the feet and groins.

A questionnaire covering these problems was sent to 120 active members of the American Dermatological Association, Inc. Eighty-eight of these questionnaires were answered and returned.

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2. Many patients are so imbued with the idea of the contagiousness and ease of transmission of ringworm that they have veritable phobias and are constantly scrubbing, using strong soaps, disinfectants, germicides and patent remedies on themselves, on their families and on all objects and utensils in their environment. These procedures naturally lead to all kinds of irritations and aggravations of existing lesions of the skin and even to production of allergic and other dermatoses, which are then again considered infectious and subjected to the same inordinate cleansing and disinfection. It is not always easy to disabuse these patients of their ideas. But once they are convinced that they are not "unclean," not a menace to themselves and to others, patients with superficial ringworm infections experience great psychic relief. And often the cure of what was apparently ringworm depends on the physician's success in bringing home to the patient the lack of contagiousness, thus eliminating the further use of the skin-damaging agents and procedures.

3. Symposium on the Practical Management of Eczematous Ringworm of the Hands and Feet (Athlete's Foot—Dermatophytosis and Dermatophytids), J. Invest. Dermat. **3**:523, 1940. Eczematous Ringworm of the Hands and Feet, editorial, J. A. M. A. **116**:1528 (April 5) 1941.

ANALYSIS OF REPLIES TO QUESTIONNAIRE

QUESTION 1.—*I have observed . . . instances of proved conjugal transmission of ringworm of the groin.*

Seventy-seven dermatologists answered this question. Of these, 62, or 80.52 per cent, answered that they had never observed a case of proved conjugal transmission; 4, or 5.19 per cent, were indefinite in their answers, and 11, or 14.29 per cent, answered that they had encountered cases of proved conjugal transmission of ringworm of the groin. On analysis of this last group, we found that in only 3 of these cases of presumptive transmission was the condition proved by culture.

These answers tend to confirm our opinion of the negligible importance of conjugal transmission of ringworm of the groin.

QUESTION 2.—*I have observed . . . instances of proved conjugal transmission of ringworm of the feet.*

Seventy-nine dermatologists answered this question. Fifty-five, or 69.25 per cent, answered that they had never observed a case in which this was proved; 8, or 10.13 per cent, were indefinite in their answers, and 16, or 20.25 per cent, answered that they had observed cases in which conjugal transmission of ringworm of the feet was proved.

These answers tend to confirm our opinion of the negligible importance of conjugal transmission of ringworm of the feet.[4]

QUESTION 3.—*I have observed . . . instances of proved other familial transmission of ringworm of the groin.*

Seventy-eight dermatologists answered this question. Sixty-one, or 78.21 per cent, stated that they had never observed a case in which this was proved; 6, or 7.69 per cent, were indefinite in their answers, and 11, or 14.10 per cent, answered that they had observed cases in which this was proved.

We concluded that our opinion is confirmed and that familial transmission of ringworm of the groin is of about the same negligible importance as is conjugal transmission of ringworm of the groin.

QUESTION 4.—*I have observed . . . instances of proved other familial transmission of ringworm of the feet.*

Seventy-six dermatologists answered this question. Forty-five, or 59.21 per cent answered that they had never observed a case in which this was proved; 14, or 18.42 per cent were indefinite in their answers, and 17, or 22.37 per cent, stated that they had observed cases in which this was proved.

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4. The figures appear to suggest that conjugal transmission of ringworm of the feet may occur somewhat more commonly than conjugal transmission of ringworm of the groins! However, when one realizes the small number of cases reported by the dermatologists questioned, one finds that the apparent difference may be simply a statistical error, and one is impressed by the rarity of the occurrence of conjugal transmission of ringworm of both the feet and the groins.

We conclude that our opinion is confirmed and that familial transmission of ringworm of the feet is of about the same negligible importance as conjugal transmission of ringworm of the feet.

QUESTION 5.—*That the eruption was due to a ringworm infection was determined (a) by purely clinical observation or (b) by microscopic demonstration of fungi.*

That the eruption was actually contracted from the conjugal partner was determined (a) by cultural proof of the identity of the fungi in both partners; (b) by the chronologic sequence (that is, the eruption in one partner shortly preceded the appearance of a clinically identical eruption in the second partner), or *(c) by other conclusive proof that the fungous infection was not simply coincidental or contracted by both partners from some other source.*

As far as the method of proof is concerned, 32 dermatologists stated that their opinions were based on purely clinical observation. Thirty-three used proof by microscopic examination; 33 used proof based on chronologic sequence; 6 attempted proof by cultural methods, and 4 mentioned proof by "other methods," which, however, were not specified. Some of the dermatologists used various types of proofs at the same time. The whole group of 88 who answered our questionnaire reported only 4 cases in which transmission was proved by identification of the fungus by cultural methods, as well as by clinical evidence and microscopic examination. (One dermatologist reported that in a "few" cases the condition had been thus proved. Another checked the pertinent squares in the questionnaire but did not specify the number of cases in which the condition was really thus proved. The answers of these 2 could of course not be used in the evaluation of the results.)

The general absence of careful clinical studies and mycologic cultural examination makes even the few cases here reported as instances of proved transmission acceptable only with some degree of reserve.

Thus, analysis of the methods of proof employed demonstrates the insignificance of the number of cases of really proved conjugal and familial transmission of ringworm infections.

QUESTION 6.—*Do you recommend to your patients any measures to prevent the conjugal or familial transmission of ringworm of the feet or groins? If so, please specify.*

Eighty dermatologists answered this question. Twenty-five, or 31.25 per cent, answered that they give no recommendations whatsoever regarding prophylactic measures; 25, or 31.25 per cent, stated that they give prophylactic recommendations of a mild general nature, and 30, or 37.50 per cent, answered that they give detailed directions for prophylactic measures to every patient suffering from a ringworm infection of the feet or groins. Thus, 25, or 31.25 per cent, give no directions for prophylaxis, while 55, or 68.75 per cent, give some directions regarding such prophylactic measures. However, there appears to be a major con-

tradiction in the fact that 68.75 per cent of the dermatologists questioned still made recommendations for prevention of transmission of ringworm infections, although 72 per cent of the same group of dermatologists stated that they had never seen conjugal or familial transmission of ringworm of the feet and groins. This suggests that in many instances prophylactic measures are recommended in order to be on the safe side, to satisfy a public demand, to satisfy referring physicians, from inertia or habit or as a placebo, rather than from the dermatologist's own conviction as to their necessity.

The last two questions of our questionnaire were designed to obtain a summary of the opinion of the participating dermatologists themselves as to the importance of conjugal and familial transmission of ringworm infections of the feet and groins.

QUESTION 7.—*In your experience, has the conjugal transmission of these types of ringworm shown itself to be of practical importance?*

Eighty-three dermatologists answered this question, of whom 63, or 75.91 per cent, stated that conjugal transmission of ringworm of the feet and groins is of no practical importance; 17, or 20.48 per cent, reported that it is rarely of importance, and 3, or 3.61 per cent, stated their belief that it is of definite practical importance.

QUESTION 8.—*In your experience, has other familial transmission of these types of ringworm shown itself to be of practical importance?*

Eighty-one dermatologists answered this question, of whom 53, or 63.43 per cent, stated that familial transmission is of no practical importance; 19, or 23.46 per cent, reported that familial transmission is rarely of practical importance, and 9, or 11.11 per cent, stated that familial transmission is practically important.

These answers tend to confirm our own opinion regarding the relative unimportance of conjugal or familial transmission in the elicitation of attacks of these common forms of ringworm.

COMMENT

The replies to our questionnaire reveal the significant fact that 88 outstanding American dermatologists, all having an immense experience in the treatment of fungous diseases, can together report a total of only 4 cases of proved conjugal or familial transmission of ringworm infection of the feet or groins. This transmission in these 4 was considered proved because, apart from the clinical impression and the chronologic sequence in which one case followed another, there was cultural proof of the identity of the fungi in the infected persons. There can be no question that there must be other additional cases in which the suspected but still unproved conjugal or familial transmission of the infection was actually due to conjugal or familial exposure. However, the extremely small total of cases of both proved and suspected transmission reported in the answers to our questionnaire confirms our impression that such

transmission must be a rare occurrence and is of little, if any, practical importance. This bears out the expressed opinion that only when for one reason or another a person becomes particularly susceptible to these micro-organisms is clinical disease produced. And as a corollary to this conclusion it appears highly probable that many of the present methods of general prophylaxis and disinfection are illogical and can serve no useful purpose.[5]

SUMMARY AND CONCLUSIONS

In contrast to the opinions held and expressed by many other competent observers, we reached the conviction that in our patients familial and conjugal exposures played no role in eliciting attacks of ringworm of the feet and groins.

This question of the manner of transmission and the causation of attacks of ringworm is always an important medical problem, since fungous infections of the feet and groins is one of the most common of human diseases. Added significance is attached to this problem at present because of the extremely high morbidity caused by these diseases in military personnel.[6] A questionnaire was prepared and circulated with the object of discovering whether the observations and opinions of the present authors were sustained or contradicted by the observations and opinions of the majority of outstanding dermatologists. Eighty-eight replies were received and are here analyzed. The answers confirm our original opinion and show clearly that conjugal and familial transmission of ordinary fungous infections of the feet and groin is either nonexistent or a great rarity. This observation leads to the conclusion that many of the most widely used present measures of prophylaxis are illogical and probably serve no useful purpose but are potentially harmful. A reorientation of opinion in regard to the causation of attacks by common ringworm is required. The results of our investigations support the concept that alterations in host susceptibility and loss of local immunity are more to blame than new exposure to exogenous micro-organisms. It is logical to assume that those prophylactic measures which stress personal and individual care and hygiene of the feet and groins will have the most prospect of success in preventing attacks of the common superficial fungous infections.

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5. This idea was expressed also by the late dean of American dermatology, Dr. William Allen Pusey, who in a letter accompanying his questionnaire stated the following opinion: "According to my experience the contagiousness of the forms of ringworm that Whitfield called attention to is greatly overestimated. The contagiousness is very slight except in a relatively few persons, and I do not know how to account for it except by a considerable immunity to it in most people, as it proves altogether trivial in a vast number of people who have it between the toes. That sort of infection is so frequent that avoiding exposure to it would be about as difficult as avoiding exposure to smoke in Chicago."

6. Sulzberger, M. B.; MacClatchie, L. K., and Parsons, R. P.: Military Dermatology and Syphilology, M. Clin. North America **11**:1677 (Nov.) 1941.

CUTANEOUS LEISHMANIASIS (ORIENTAL SORE) IN THE UNITED STATES AND CANADA

A SURVEY OF THE LITERATURE AND REPORT OF FOUR CASES

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Since the classic paper of Wright,[1] in which was delineated for the first time the precise morphologic picture of Leishmania tropica, there have been 24 cases of cutaneous leishmaniasis reported in the United States and Canada. None of these is claimed to be autochthonous, all having been imported from Iraq, Iran, Armenia, Palestine, Syria, Italy or India.

There are three forms of leishmaniasis: (*a*) visceral (kala-azar), (*b*) mucocutaneous, or American,[2] and (*c*) cutaneous. This report is concerned only with the form classified as cutaneous.

This disease is rife in Asia Minor and in the southern Mediterranean countries. Baghdad, Iraq, where it is practically universal, is the largest endemic center in the world.[3] Other endemic centers are: Aleppo, Syria; Crete; Cyprus; Delhi, India; Lahore, India; Kandahar, Afghanistan, and Jericho, Palestine. As a result, synonymous local terms, such as "Baghdad button," "Aleppo boil" and "Lahore sore," have come into common usage. Among other names for the same disease are oriental sore, tropical ulcer and *bouton d'orient*.

One may reasonably expect this disease to be a souvenir of many men in the armed forces of Great Britain, Germany and Italy who have been in the Near East.

Cutaneous leishmaniasis begins as a papule on the face, neck, hand, leg or other exposed part. The surrounding area is erythematous, and the lesion may at first resemble an insect bite. There is no pain or tenderness. The next stage is the development of an ulcer at the site

1. Wright, J. H.: Protozoa in a Case of Tropical Ulcer (Delhi Sore), J. M. Research **10**:472-482, 1903.

2. This form occurs mainly in South and Central America and is known by a great many different local names. It differs from oriental sore in the following ways: There is often seen invasion of the mucosa of the nose and mouth; it may last for many years if untreated; there is little tendency toward spontaneous cure; death may follow in cases in which the condition is severe and permanent immunity does not follow an attack (Fox, H.: American Leishmaniasis, Arch. Dermat. & Syph. **23**:480-501 [March] 1931).

3. Akrawi, F.: Local Treatment of Ulcerated Oriental Sore by Powder of Sulphonamide Derivatives, J. Trop. Med. **43**:46 (Jan. 1) 1940.

of the papule. This has sharp edges, a raised and indurated border and granulation tissue at the base. A heavy brown crust appears over the ulcer and serous fluid is discharged. Similar lesions often develop by autoinoculation on other parts of the body. After the ulcer heals it leaves a tough white depressed scar. Splenomegaly is not characteristic of the disease.[4]

Cutaneous leishmaniasis is caused by L. tropica and is carried by a vector thought to be the sand fly (Phlebotomus) or the bedbug.[5] Patton [5b] claimed that transmission directly from man to man does not occur in nature, though actual infection by intent has been accomplished experimentally.[6]

The incubation period is said to vary from a few weeks to three years,[7] although it is more likely to be from two to six months.[8]

The microscopic appearance of all the strains of Leishmania is for practical purposes identical. It is an oval or round body 2 to 4 microns in diameter containing a small round nucleus (trophonucleus) and a short rodlike blepharoplast.[4a] Great numbers of the bodies are often present in various stages of disintegration in the large mononuclear cells. Leishmania can be grown on N.N.N. medium.[4a] The tropica form has flagella and leptomonad characteristics when cultured.

In the early stages of ulceration the parasite may be seen readily by smearing the discharge on a glass slide and using Giemsa stain. When the ulcer is older and secondarily infected the leishmanias usually can be found only by puncturing the edge of the ulcer with a capillary pipet or by biopsy. The diagnosis outside of endemic areas should be made

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4. (*a*) Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 2, Philadelphia, Lea & Febiger, 1940. (*b*) Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, ed. 3, New York, William Wood & Company, 1919. (*c*) Rolleston, H.: British Encyclopedia of Medical Practice, London, Butterworth & Co., Ltd., 1938, vol. 7. (*d*) Manson-Bahr, P. H.: Manson's Tropical Diseases, ed. 11, Baltimore, William Wood & Company, 1940.

5. (*a*) Southwell, T., and Kirschner, A.: On the Transmission of Leishmaniasis, Ann. Trop. Med. **32**:95-102 (April) 1938. (*b*) Patton, W. S.: Some Reflections on the Kala-Azar and Oriental Sore Problems, Indian J. M. Research **9**:495-532, 1922. (*c*) Manson-Bahr.[4d]

6. Parrot, L.: Sur la contagion directe de bouton d'Orient, Compt. rend. Soc. de biol. **100**:467, 1929. Adler, S., and Theodor, O.: Experimental Transmission of Cutaneous Leishmaniasis to Man from Phlebotomus Papatasii, Ann. Trop. Med. **19**:365-371 (Sept.) 1925; Transmission of Leishmaniasis from Artificially Infected Sandflies to Man, ibid. **21**:89-110 (July) 1927; Attempts to Transmit Leishmania Tropica by Bite: Transmission of L. Tropica by Phlebotomus sergenti, ibid. **23**: 1-18 (April) 1929; Additional Evidence of Occurrence of L. Tropica in Wild Phlebotomus Papatasii, ibid. **23**:19-21 (April) 1929.

7. Napier and Halder, cited by Castellani and Chalmers.[4b]

8. Roberts, R. W.: Cutaneous Leishmaniasis, J. Trop. Med. **38**:24 (Jan. 15) 1935. Rolleston.[4c]

only on the discovery of the parasite. It is preferable to search smears for leishmanias before performing a biopsy, as the bodies are more easily seen in the former. Furthermore, the histologic specimens may at times be confusing and may strongly suggest squamous cell carcinoma,[9] endothelioma,[10] epithelioma,[11] Boeck sarcoid [12] and tuberculosis.[13]

Since cutaneous leishmaniasis is a self-limiting disease which usually clears up within a year, evaluation of the efficacy of therapeutic measures is difficult. Among the usual treatments are application of antiseptic ointments and washings, administration of antimony preparations parenterally or their injection beneath the ulcer, cauterization, roentgen irradiation and freezing with solid carbon dioxide.[14] The latter two methods seem to be in favor at present.

COMMENT ON THE LITERATURE

There are 24 cases of cutaneous leishmaniasis reported from the United States and Canada.[15] None of these cases may be termed

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9. Macadam, W.: Histological Resemblances of Oriental Sore to Epithelioma, Brit. J. Surg. **7**:487-489 (April) 1920.

10. Smith, D. K.: Oriental Sore, Arch. Dermat. & Syph. **5**:69-72 (Jan.) 1922.

11. Thomson, J. G.: Pathology of Oriental Sore and Espundia, Proc. Roy. Soc., Med. **26**:179-180 (Dec.) 1932.

12. Dupont, A.: Leishmaniose cutanée à structure histologique de sarcoïde de Boeck, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **41**: 1291-1294 (June) 1934.

13. MacLeod, J. M. H.: Lupoid Variety of Cutaneous Leishmaniasis, J. Trop. Med. **37**:358-359 (Dec. 1) 1934. Thomson.[11]

14. (*a*) Barr, D. P.: Modern Medical Therapeutics, Baltimore, Williams & Wilkins Company, 1940, vol. 2. (*b*) Warma, J. D.: Oriental Sore, Indian M. Gaz. **66**:383-388 (July) 1931. (*c*) Manson-Bahr.[4d]

15. (*a*) McEwen, E. L.: Oriental Sore in the Americas with Report of a Case, J. Cutan. Dis. **32**:275, 1914. (*b*) Spencer, R. D.: A Case of Oriental Sore of Italian Origin Encountered in the United States, J. A. M. A. **76**:1494 (May 28) 1921. (*c*) Fox, H.: Oriental Sore, New York M. J. **116**:365-367 (Oct. 4) 1922. (*d*) Faber, H. K., and Schussler, H., Jr.: Leishmaniasis in the United States, J. A. M. A. **80**:93-97 (Jan. 13) 1923. (*e*) Lambert, R. A.: Oriental Sore (Cutaneous Leishmaniasis) in the United States, ibid. **80**:986-989 (April 7) 1923. (*f*) Guy, W. H., and Jacob, I. M.: Aleppo Boil, Arch. Dermat. & Syph. **14**:361 (Sept.) 1926. (*g*) Andrews, J. M.: Report of Case of Oriental Sore in the United States, Am. J. Trop. Med. **7**:221-224 (July) 1927. (*h*) Roberts, F. W.: Cutaneous Leishmaniasis: Report of Two Cases, Arch. Dermat. & Syph. **30**:401-408 (Sept.) 1934. (*i*) Hedge, H. M.: Leishmania Tropica, ibid. **31**:745 (May) 1935. (*j*) Trow, E. J.: Oriental Sore: Report of Case, ibid. **35**: 455-459 (March) 1937. (*k*) Cole, H. N., and Driver, J. R.: Oriental Sore ("Aleppo Boil"), ibid. **37**:332 (Feb.) 1938. (*l*) Parounagian, M. B.: Oriental Sore Involving Brother and Sister, ibid. **37**:531-532 (March) 1938. (*m*) Templeton, H. J.: Oriental Sore, ibid. **41**:990-991 (May) 1940. (*n*) Hopkins, J. G.: Oriental Sore, ibid. **43**:1033 (June) 1941. (*o*) Ewing, J.: Personal communication to the author. (*p*) Wright.[1] (*q*) Smith.[10]

autochthonous, as all the patients had been at one time near the reservoirs of the disease. Hence one may expect the incidence in this country to vary with the volume of immigration from endemic areas. In 1938 and 1939 a total of 2,357 persons entered the United States from Palestine.[16] There are annual quotas of 100 from Iraq, Iran, Arabia, Egypt and India.

Seventeen of the patients, including those of my own, were 18 years of age or younger. The majority of patients with this condition seen in endemic areas are children aged from 6 months to 3 years.[17] However, since it may be assumed that the traveling portion of the population is older, it is not surprising that in the 28 cases covered by this report the average age is about 22.

With 1 exception [15d] the lesions occurred on the exposed parts of the body. Twelve patients had ulcers of the face, cheek or ear.

Although McEwen [15a] called the condition in his case oriental sore, the lesion may not have been true cutaneous leishmaniasis. His patient noticed the lesion after visiting South America, where the mucocutaneous form is prevalent; the ulcer was resistant to therapy (unlike oriental sore). Furthermore, the distinction between the two forms had not yet been made at that time. It is true that there were no mucosal lesions in this case, but that does not exclude the American type, as there is mucosal involvement in only 15 to 20 per cent of those cases.[18]

REPORT OF CASES

CASE 1.—Y. K., a white girl, born in August 1934 in Teheran, Persia, first visited Baghdad, Iraq, in April 1937. She stayed there eleven months and then returned to Teheran. She revisited Baghdad from May until July 1940 and then left on an eastward airplane trip to the United States. She made the following stops on the way: Basra, Iraq; Karachi, India; Calcutta, India; Rangoon, Burma; Bangkok, Thailand; Hong Kong, China; Manila, Philippine Islands, and Honolulu, Territory of Hawaii. She arrived in the United States on Sept. 9, 1940, and on September 20 her parents noticed a small red pimple on her right cheek. There was no recollection of an insect bite. The incubation period thus seems to have been between two and four months.

The patient had had chickenpox and measles. Diphtheria toxoid and cholera and smallpox vaccinations had been given. Her only sibling, a 2 year old girl, had not contracted the disease.

Physical examination on September 24 revealed a white girl with an infection of the upper part of the respiratory tract. On the right side of the face over the zygoma there was a red indurated nontender swelling, 2 cm. in diameter, surmounted by two white papules. There was a similar lesion, 1 cm. in diameter, on the left side of the glabella.

16. The British Library of Information: personal communication to author.

17. Akrawi.[3] Manson-Bahr.[4d]

18. Fox, H.: American Leishmaniasis, Arch. Dermat. & Syph. **23**:480-501 (March) 1931; cited by Roberts.[15h]

Summary of Cases of Cutaneous Leishmaniasis

Case	Authors	Age, Sex	Incubation Period	Place of Acquisition	Place of Diagnosis	Location of Lesion	Duration of Disease	Method of Diagnosis	Laboratory Data	Treatment	Result
1	Wright [1].....	9 F	Not given *	Armenia	Boston	L. cheek	Not given	Biopsy	Not given	Excision	Not given
2	McEwen [15a].....	37 M	Not given	South America	Chicago	L. ear	Not given	Smear, biopsy	Wassermann —; tuberculin +	Zinc ointment, ichthammol and solid carbon dioxide	Some improvement with solid carbon dioxide
3	Ewing [15e].....	Young M	Not given	Not given	New York (city)	Forehead	Not given	Biopsy	Not given	Not given	Not given
4	Spencer [15b].....	18 M	Not given	Italy	Ashland, Pa.	R. cheek, l. wrist	Not given	Smear, biopsy	Urine and sputum normal; Wassermann and tuberculin —; RBC. 4,710,000; WBC. 10,800; blood negative for parasites	Solid carbon dioxide, roentgen rays	Cured
5	Smith [10].....	4 M	Not given	Baghdad, Iraq	Toronto, Canada	Both cheeks, l. ear	6 mo.	Smear	Not given	Various local treatments, roentgen rays and neoarsphenamine	Healed four weeks after neoarsphenamine
6	Smith [10].....	Adult F	Short time	Baghdad, Iraq	Toronto, Canada	R. cheek	Not given	Smear	Not given	None	Not given
7	Smith [10].....	8 F	10 wk.	Baghdad, Iraq	Toronto, Canada	L. ear	Not given	Smear	Not given	None	Not given
8	Smith [10].....	40 M	Not given	Baghdad, Iraq	Toronto, Canada	L. wrist	Not given	Smear	Not given	None	Not given
9	Fox [15c].....	12 M	Not given	Aleppo and Beirut, Syria	New York (city)	Face	Not given	Biopsy	Wassermann —; urine normal	Not given	Not given
10	Fox [15c].....	57 M	Not given	Iran, Iraq and India	New York (city)	Hand, neck	Not given	Biopsy	Wassermann —; urine normal	Solid carbon dioxide	Not given
11	Faber and Schussler [15d]	6 M	Not given	Baghdad, Iraq	San Francisco	L. buttock	1 yr.	Scrapings	Not given	2% antimony and potassium tartrate ointment, creosote and ointment of mercuric nitrate	No effect from first; second followed by cure
12	Lambert [15e].....	17 Not given	About 8 mo.	Aleppo and Beirut, Syria	New Haven, Conn.	L. ankle	Not given	Smears, biopsy	Wassermann —; WBC. 8,800	Three roentgen ray treatments and skin grafting	Cured in 1 month

13	Lambert [15e]	15 F	Not given	Asia Minor	New Haven, Conn.	R. arm, l. wrist	1 yr.	Smears negative †	Not given	Red mercuric oxide	Healed in 1 year
14	Guy and Jacob [15f]	19 M	Not given	India	Pittsburgh	R. cheek, r. forearm	Not given	Smears negative; result of biopsy positive	Wassermann —	Antimony and potassium tartrate intravenously	Healed
15	Andrews [15g]	Young M	Not given	Dyar-Bekir ‡	Baltimore	R. finger	Not given	Smear	Not given	Silver nitrate, neoarsphenamine and antimony and potassium tartrate	None §
16	Roberts [15h]	16 M	Over 8 mo.	Armenia	New Haven, Conn.	Leg	Not given	Microscopic study	Not given	Roentgen rays and local compresses	Healed
17	Roberts [15h]	10 Not given	Not given	Palestine	New Haven, Conn.	L. shoulder	2 yr.	Microscopic study	Not given	Emetine hydrochloride, various compresses and two excisions	Second excision followed by cure
18	Hedge [15i]	27 F	Not given	? Crete	Chicago	R. arm	Over 1 yr.	Smear	Wassermann and Kahn —; urine normal; RBC. 3,920,000; WBC. 7,500; hemoglobin 70%	Not given	Not given
19	Trow [15j]	56 F	Not given	India and Iraq	Toronto, Canada	L. arm (? elbow, abdomen)	Not given	Biopsy	Wassermann —; urine normal	Antimony intravenously, roentgen rays and emetine hydrochloride	Rapid cure
20	Cole and Driver [15k]	35 F	2 mo.	Baghdad, Iraq	Cleveland	Both forearms	Over 8 mo.	Smears, biopsy	Not given	Roentgen rays and fuadin intravenously	Not given
21	Parounagian [15l]	8 M	Not given	Aleppo, Syria	New York (city)	Face and l. leg	9 to 10 mo.	Not given	Not given	Not given	Not given
22	Parounagian [15l]	11 F	Not given	Aleppo, Syria	New York (city)	Nose	8 mo.	Not given	Not given	Not given	Not given
23	Templeton [15m]	35 F	4 mo.	Beirut, Syria	Oakland, Calif.	R. thigh	Over 2 mo.	Culture	Not given	None	20% of ulcer healed after 2 months
24	Hopkins [15n]	5 F	2 mo.	Teheran, Persia, or Delhi, India	New York (city)	L. cheek	Over 2 mo.	Puncture	Not given	Not given	Not given

* "Not given" indicates information was not given by the authors.
† "There is no doubt about the diagnosis."[15e]
‡ Endemic center.
§ Treatment stopped because patient wished to acquire natural immunity.

The red blood cell count was 4,960,000; the hemoglobin content, 14 Gm.; the white blood cell count, 10,800, and the differential count, 66 per cent polymorphonuclear leukocytes, 36 per cent lymphocytes, 4 per cent monocytes and no eosinophils. The urine was normal.

During the next ten days the papules on the cheek coalesced and became crusted, as did the lesion on the glabella. The crusts were removed, and the exuding serum from the underlying ulcers was smeared and prepared with Giemsa stain (forty minutes with 1:10 dilution). Leishmanias and engorged monocytes were found in abundance.

Two months after the initial lesions appeared three other similar lesions developed on the right arm and right leg. Within two weeks these began to ulcerate.

Treatment consisted of seven applications of solid carbon dioxide at approximately two week intervals, the duration of the treatments starting with ten seconds and increasing to forty seconds. One unfiltered roentgen ray treatment of 75 r was given on November 8.

Five months after the institution of treatment all the lesions were healed, leaving somewhat roughened scar tissue.

Case 2.—F. S., a 15 month old white boy, was born in Paris, France. At the age of 3 months he was taken to Baghdad, Iraq, where he stayed seven months. On Nov. 20, 1940, six and one-half months after his arrival in Baghdad, his parents noticed a small red pimple on his fourth left finger near the base of the nail. The incubation period was therefore under six and one-half months. Two weeks later he was taken on an eastward plane and boat voyage to the United States. He arrived in New York on March 17, 1941. On April 29, five months after the initial lesion appeared, another pimple was noticed on the right cheek.

There was no history of insect bite. Further past history is not contributory.

The patient was first seen by me on May 13, 1941, and he was in apparent robust health except for having the local lesions.

His temperature was normal. The red blood cell count was 4,980,000; the hemoglobin content, 13 Gm.; the white blood cell count, 10,500, and the differential count, 46 per cent polymorphonuclear leukocytes, 45 per cent lymphocytes, 4 per cent monocytes, 1 per cent basophils and no eosinophils. The reaction to a Mantoux test was negative, and the urine was normal.

On the dorsal aspect of the left fourth finger, extending from the base of the nail proximally for 1 cm., there was a hard brown nontender crust. Underlying this was a shallow moist ulcer with granulations. Much serum was present. On the cheek was a white papule, 1 mm. wide, surrounded by a zone of erythema.

Specimens of serum taken from the edge of the ulcer on the finger with the aid of capillary pipets showed typical leishmanias and engorged mononuclear cells when prepared with Giemsa stain. No attempt was made to puncture the lesion on the face.

Treatment consisted of two applications of solid carbon dioxide to the face and three to the finger, following Warma's technic.[14b] These were given at one to two week intervals, and 3 per cent ammoniated mercury ointment was prescribed for daily application.

Three weeks after the beginning of treatment all signs of activity had disappeared. The finger showed a healthy layer of new epithelium, and the papule of the face had entirely disappeared, leaving a somewhat depigmented area 0.5 cm. in diameter.

CASE 3.—G. S., a white boy, was born in Brussels, Belgium, on April 3, 1935. He was in Baghdad, Iraq, from Dec. 22, 1939 to Feb. 6, 1941, leaving on the latter date for the United States. He traveled by plane and ship and did not pass through areas known to be endemic.

He had been given diphtheria toxoid and cholera and smallpox vaccinations. There was no history of insect bite. The past history was otherwise irrelevant. Of 2 siblings, 1 contracted the disease (case 4).

The first sign of the disease was noticed on Feb. 8, 1941. Thus, there was an indefinite incubation period of under thirteen months.

Physical examination on April 5 revealed no abnormalities except the local lesion. In the right buccal area there was a hard brown crust 1 cm. in diameter. This covered a shallow ulcer typical of cutaneous leishmaniasis. There were no other lesions.

Specimens of serum removed with the aid of capillary pipets showed typical leishmanias and engorged monocytes. The red blood cell count was 4,990,000; the hemoglobin content, 15 Gm.; the white blood cell count, 7,500, and the differential count, 52 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes, 23 per cent monocytes and no eosinophils. The urine was normal. The reaction to a Mantoux test was negative.

Treatment consisted of three applications of solid carbon dioxide at weekly intervals, by Warma's technic. Three per cent ammoniated mercury ointment was applied daily. Three weeks after treatment was begun the ulcer had entirely disappeared and the area was covered with healthy epithelium.

CASE 4.—N. S., a sister of G. S. (case 3), was born in Brussels, Belgium, on Sept. 9, 1931. She first went to Baghdad, Iraq, in 1933 and stayed for seven months. Then she went back to Brussels. She revisited Baghdad from Dec. 22, 1939 to Feb. 6, 1941, leaving on the latter date with her brother (case 3) for the United States.

The first sign, a papule on the left wrist, was noticed in January 1941. Thus there was an indefinite incubation period of about a year or less.

She had had no serious illnesses, nor was there any history of insect bite. She received the same inoculations as her brother. The past history was otherwise irrelevant.

When first seen by me on June 4, 1941 she was apparently normal except for having the sore on the dorsum of the left wrist. The ulcer was 2 cm. in diameter and typical of cutaneous leishmaniasis. The child had previously removed the crust. Smears of material taken with a capillary pipet showed an abundance of leishmanias and engorged monocytes when prepared with Giemsa stain.

The red blood cell count was 5,000,000; the hemoglobin content, 15.5 Gm.; the white blood cell count, 8,000, and the differential count, 62 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes, 8 per cent monocytes and no eosinophils. The reaction to a Mantoux test was negative; the urine was normal. The sedimentation rate (Cutler method) was 9 mm. per hour. The following components of the blood were of normal amount; total serum protein, serum albumin, globulin, euglobulin, cholesterol and nonprotein nitrogen. The cephalin flocculation test gave negative results.

Treatment consisted of three applications of solid carbon dioxide for ten to twenty seconds, according to Warma's technic. These were given in the space of a month and were followed at first by flattening of the ulcer. At the same time the

area involved became several times as large in diameter; but the activity subsided, and at the time of writing (five weeks after treatment was begun) the ulcer is almost completely healed.

SUMMARY AND CONCLUSIONS

The cause and distinguishing features of cutaneous leishmaniasis are discussed.

Twenty-four cases of cutaneous leishmaniasis reported in the United States and Canada have been collected from the literature, to which are added 4 others.

The disease is one of Near Eastern origin, and as seen here occurs predominantly in the first two decades of life.

One may expect that an influx into endemic areas of groups, such as expeditionary armed forces, which do not possess the immunity conferred by previous attack will be followed by the appearance of the disease in these groups.

The presence of an ulcer of the face or extremities of one who has been in the Near East within three years should arouse suspicion of cutaneous leishmaniasis.

Dr. H. B. Shookhoff confirmed the observations on the smears.

The chemical examination of the blood and the cephalin flocculation test were made at the Presbyterian Hospital.

66–20 One Hundred and Eighth Street.

LUPUS ERYTHEMATOSUS

CLINICAL OBSERVATIONS IN FOUR HUNDRED AND FORTY-THREE CASES

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During the past five years at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital there have been 443 patients with a diagnosis of lupus erythematosus. As 153,475 patients were treated during this period, the general incidence of the disease was 0.28 per cent.

CLASSIFICATION OF PATIENTS AND CLINICAL OBSERVATIONS

Sex.—There were 184 men (41 per cent) and 259 women.

Age.—There were no patients below the age of puberty.[1] A boy of 17 with disseminated chronic lesions had been treated eleven years previously for the same disease. The incidence rose regularly to reach a peak at about 40 years of age and then fell off again. It was rare in old age; only 20 patients were 60 or over. More than half of the patients were between 30 and 50 years of age.

Race.—In 1936 there was 1 Negro patient with the disease; in 1937, 2; in 1938, none, and in 1939, 6. For 1940 I made no record of this item. The hospital keeps no record of the total number of Negro patients per annum. It is probable, though, that the disease was seen less often, relatively, among them than among the white patients.

Occupation.—Most of the women affected were housewives. One might expect the disease to be more common among patients who had outdoor trades. Such was not the case. Of the 263 patients a record of whose occupation was kept, only 2 were seamen and another was a gardener. As New York is one of the world's great ports, it is likely that more seamen would have been seen with the disease if it were more common among them than it is in the population at large.

Seasonal Incidence.—According to the date of the first visit, there did not seem to be any particular type of seasonal variation in the occurrence of the disease.

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Dr. George Miller MacKee, Director.

1. Dr. Fred Wise, one of the chiefs at the clinic, to whom I showed my manuscript, commented that within the past few months (the year 1941 was not included in this survey) he had seen 3 patients under 6 years of age at the clinic.

Duration at the Time of the First Visit.—The patient almost never appeared at the clinic before two months had elapsed. This was so even in cases of the disseminated type. Often the patient had already received treatment elsewhere. In about 50 per cent of the cases the lesions were more than a year old at the time of the first visit.

Type of Disease.—In the great majority of the patients the condition was of the chronic discoid type. Only 22 (5 per cent) had disseminated lesions. I made no attempt to classify the conditions into the acute, subacute and chronic types, because it was frequently impossible to decide from reading the history.

Number of Patches.—In 67 instances (15 per cent) there was only one patch.

Location of the Eruption.—A diagnosis of lupus erythematosus was not made in any case in which there were no lesions on the face, scalp

Incidence of Lupus Erythematosus According to Sex and Age

Year	Total New Patients	Patients with Lupus Erythematosus	Men	Women	Age in Years					
					10-19	20-29	30-39	40-49	50-59	60 and Over
1936	34,091	89	42	47	2	22	35	18	12	0
1937	30,500	92	40	52	4	26	22	22	11	7
1938	30,604	87	33	54	5	17	19	29	12	5
1939	29,695	84	35	49	5	22	23	17	11	6
1940	28,615	91	34	57	6	19	28	27	9	2
Totals	153,475	443	184	259	22	106	127	113	55	20

or neck. I have not tabulated the number of times that each part of the body was affected, because too frequently when there were multiple lesions the physician who took the history did not specify the exact locations. The commonest sites by far were the nose and cheeks; they were involved in about half of the cases. The third most common location was probably the scalp. The ears, forehead, eyelids, chin, mucous membranes of the face, neck and hands followed approximately in that order. If there were lesions elsewhere the condition was almost always of the disseminated type. The mucous membranes of the face were mentioned in about 10 per cent of the cases.

Therapy.—One hundred and fifty-three patients attended the clinic less than four times (34 per cent). Of those who attended four or more times, almost all were treated with gold or bismuth preparations or vaccines. There was improvement in 38 patients of 81 given a gold compound intravenously; good results were obtained in 55 of 170 patients given a bismuth compound intramuscularly, and 9 out of 21 given vaccines showed improvement (the proportion of good results would have been higher if the count had been limited to those who had received

at least eight or ten injections instead of only four). The trend during the time covered by this study was away from gold and toward bismuth therapy. In 1936, 22 patients received bismuth and 30 gold; in 1940 40 were given bismuth and only 6 gold.

Almost anything might be expected during the course of treatment. Occasionally new lesions appeared after the old ones had improved or even disappeared completely. Sometimes as many as sixty or seventy injections had no effect on the patient.

SUMMARY

During the past five years at the clinic about 1 new patient in 350 had a diagnosis of lupus erythematosus. Three fifths of the patients were women. Most of the patients were over 30 years of age. The patient almost always waited several months before going to the clinic for treatment. Only 9 patients in four years were Negroes. Season and occupation played no part in determining the frequency of occurrence of the disease. In decreasing order of frequency of site, lesions were seen on the nose, cheeks, scalp, ears, forehead, eyelids, chin, mucous membranes of the face, neck and hands. About 1 patient in 20 had disseminated lesions; about 1 in 7 had a single patch. Approximately one third of the patients failed to return after one, two or three visits to the clinic; of the remaining two thirds, one third were benefited by therapy (i. e., 2 patients out of every 9 in the entire series). Gold was not appreciably more effective as a therapeutic agent than bismuth or vaccines.

12 West Forty-Fourth Street.

ARTIFICIAL FEVER THERAPY IN JUVENILE NEUROSYPHILIS

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AND

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Since a review of the literature on juvenile dementia paralytica from January 1936 on reveals little or no reference to the use of artificial fever therapy and no specific reference to results, we feel that publication of our small series would be of interest to the members of the medical profession.

In Menninger's comprehensive monograph on juvenile dementia paralytica [1] no reference was made to the use of fever therapy except that of malaria. This author considered the outlook in this disease as unfavorable under any type of treatment but stated that malaria may produce a more persistent and more complete remission than chemotherapy. He pointed out that chemotherapy should always follow the course of malaria. Bennett, Nielsen, Fechner and Cash [2] indicated in 1939 that they had tried it in 1 case. There have been many uses of fever therapy in its various forms, in particular, malaria.[3] It is interesting to note that there have been several cases in which epilepsy has appeared during treatment of one sort or another, as recorded by Donnadieu [4] and by Roger and Alliez.[5] In our short series of cases the fever therapy was in each case produced by the use of the Kettering hypertherm.

We are reporting a study of 5 patients between the ages of 11 and 20 years at the time of their admission to the hospital. Of these 5, 4

From Hastings State Hospital.

1. Menninger, W. C.: Juvenile Paresis, Baltimore, Williams & Wilkins Company, 1936.

2. Bennett, A. E.; Nielsen, J. C., and Fechner, A. H.: Nebraska M. J. **25**:1-5 (Jan.) 1940. Bennett, A. E.; Nielsen, J. C.; Fechner, A. H., and Cash, P. T.: Arch. Phys. Therapy **20**:620-627 (Oct.) 1939.

3. Julius, W.: Deutsche Ztschr. f. Nervenh. **145**:110-115, 1938. Boeters, H.: München. med. Wchnschr. **84**:935-936 (June 11) 1937.

4. Donnadieu, A.: Ann. méd.-psychol. (pt. 2) **96**:424-429 (Oct.) 1938.

5. Roger, H., and Alliez, J.: Ann. méd.-psychol. (pt. 2) **96**:767-776 (Dec.) 1938.

showed a picture of dementia paralytica predominantly, the fifth presenting a purely tabetic picture with the exception of a typical dementia paralytica colloidal gold curve of the spinal fluid. The symptoms existing in these cases could be traced back from one to five years. One patient had previously been treated by injections of pyrifer (a nonspecific protein mixture prepared with extracts of fever-producing bacteria [colon bacilli] of nonpathogenic stocks) and administration of arsenicals (since this patient died during treatment, the history is not reported in detail).

Four of the 5 patients received a complete course of artificial fever therapy in the Kettering hypertherm, consisting of fifty hours with a temperature of 105 to 106 F., given in ten to eighteen sessions. One patient received an additional course of thirty hours about two and a half years after the first course. One patient died during his twelfth treatment, the autopsy showing the cause of death to be edema of the brain and subarachnoid hemorrhage. During the course of fever therapy all patients received weekly intramuscular injections of bismuth subsalicylate and intravenous injections of mapharsen in adequate doses, the mapharsen being administered at the height of the fever. After the last fever treatment in each case the same chemotherapy was continued for six weeks. After this, regular courses of arsenical and bismuth preparations have been used up to the time of this report.

In each case in which it was possible the patient's condition, including serologic examination of the blood and spinal fluid, was checked at intervals of six months. The 4 surviving patients have been closely observed for from one to three and a half years following the fever therapy. At the time of writing all 3 patients with dementia paralytica are at home and all of them have shown definite improvement in both physical and mental activity. The condition of the tabetic patient after about one year of improvement has remained stationary, except that the atrophy of his optic nerve has progressed practically to the point of blindness.

The Wassermann reaction of the blood of each patient was positive before treatment and remained so during subsequent checks. The Wassermann reaction of the spinal fluid was positive in 3 and weakly positive in 1 before treatment; in 3 patients it returned to normal immediately and in 1 (the tabetic patient) after two years. One of the patients whose reaction returned to normal had a positive reaction at a later date.

REPORT OF CASES

CASE 1.—D. C., an 11 year old white girl, exhibited increased "nervousness" over a period of several years. During the last few months prior to admission she became restless and sleepless. Two months before admission the left leg, left arm

and left side of her face showed transitory numbness, and short-lasting disturbances in speech, probably petit mal attacks, occurred. She was sent to the hospital by her family physician because of positive serologic reactions. She was admitted to Hastings State Hospital in December 1937, showing predominantly intellectual retardation (intelligence quotient 68). All her performances were slow, and all responses were retarded. Physically there was a slight irregularity of the pupils, which were fixed to light. There was an optic neuritis in the left eyeground. Tendon reflexes were mildly hyperactive on the left. There was moderate dysarthria. The Wassermann reactions of the blood and spinal fluid were strongly positive. The globulin content of the spinal fluid was increased. There were 72 cells per cubic millimeter in the spinal fluid and a typical dementia paralytica gold curve. From January to March 1938 she received fifty hours of fever therapy and with each treatment 0.015 to 0.02 Gm. of mapharsen. On completion of the fever therapy, the Wassermann reaction of her blood was still positive, but the reaction of her spinal fluid was doubtfully positive. The globulin content and cell count were normal, and the colloidal gold curve remained typical of dementia paralytica. Both physically and mentally there was no noticeable immediate change of her condition except perhaps that her general interest was improved and her initiative increased. The left-sided numbness had disappeared. She was paroled home and received continuous thio-bismol and tryparsamide medication. She continued to go to school, where she made a fair adjustment and passed each year. In June 1940, approximately two and a half years after the first fever course, she was given an additional thirty hours of fever therapy, the chief reason for this being that although she had continued to receive chemotherapy regularly, the serologic reactions of the blood and spinal fluid remained positive on each check-up (it is to be noted that the serologic reactions of her father, who was also syphilitic, likewise remained positive regardless of treatment). This course of treatment was also tolerated satisfactorily, but it did not result in any change of serologic reaction, even after continuous follow-up chemotherapy. The patient remained in an improved physical and mental condition and in June 1941 graduated from grade school, having adjusted herself well at home and having made plans to attend high school in the fall. Her intelligence quotient was well above the level of 80.

Case 2.—G. W., a 20 year old white youth, had difficulty in walking, which developed one year prior to admission to the Hastings State Hospital. He would occasionally lose his balance, weave and stagger, and as a result it became increasingly difficult for him to walk in the dark. Because the family physician discovered positive serologic reactions he was admitted to the hospital in April 1939, where it was found that mentally he fell within the limits of normal. However, the physical examination showed decided swaying in a standing position and a positive Rhomberg sign. The pupils were fixed, and there was partial blindness of the right eye caused by atrophy of the optic disk. There were tremor of the lips, tongue and fingers, an absence of all tendon reflexes, an absence of abdominal reflexes on the right side and a definite impairment of sense of position. The laboratory examination showed positive serologic reactions of the blood and spinal fluid, a cell count of 36 and a typical dementia paralytica colloidal gold curve of the spinal fluid. From May to August 1939 he received fifty hours of fever in thirteen treatments. The treatments were complicated twice by the development of edema of the brain and were prolonged by the occurrence of orthostatic albuminuria. With each weekly treatment he received 0.06 Gm. of mapharsen and 0.10 Gm. of bismuth subsalicylate. Following the course of fever

therapy there was decided improvement of all symptoms, particularly of the ataxia, although some uncertainties of gait persisted. Deep and superficial reflexes remained unchanged. He was paroled home in November 1939, where he remained, receiving chemotherapy continuously. Serologic examination in September 1940 still showed a positive Wassermann reaction of the blood and a dementia paralytica gold curve but a negative Wassermann reaction of the spinal fluid. The ataxia was slightly improved. Atrophy of the optic nerve had not progressed; the mental condition was entirely normal, and he had made a fair home and occupational adjustment. When he was seen again in July 1941 he had given up any occupation because of a decided loss of vision in both eyes due to atrophy of the optic nerves. During the interval at home, arsenical administration was discontinued because of toxic effect on the gastrointestinal system and the optic nerve, but the bismuth medication was maintained. Examination on the last-mentioned date revealed an unchanged physical condition except for atrophy of the optic nerves, which caused poor vision and external strabismus of the right eye. His mental condition remained entirely normal, as noted on previous occasions. The Wassermann reaction of the blood was still positive, but that of the spinal fluid had returned to normal in all tests.

Case 3.—N. A., a 17 year old white boy, two years prior to his admission to the hospital had had a basal skull fracture with delirium. One year prior to admission epileptiform seizures had developed followed by periods of unconsciousness and numbness on one side of his face. During the last two months a severe defect of memory and an increased psychomotor activity with impairment of speech had developed, and for days he had persistently remained in a noisy, confused condition. As in all the cases, there was a history of syphilis in the family. He was admitted to the Hastings State Hospital in November 1939 and showed confusion, flight of ideas and increased psychomotor activity with extreme euphoria and talkativeness. His sensorium showed gross defects. There was dysarthria, and there was a complete lack of any judgment or insight. Physically there were a tremor of the tongue and of the extended fingers and mildly hyperactive reflexes. There was decided ataxia. The laboratory data included a positive Wassermann reaction of the blood and a questionable Wassermann reaction, increased globulin content and a normal colloidal gold curve of the spinal fluid. From December 1939 to April 1940 he received fifty hours of fever therapy and seventeen weekly injections of 0.1 Gm. of bismuth subsalicylate and 0.04 Gm. of mapharsen. After the fever therapy he continued to receive routine chemotherapy. It was found after the fever therapy that his condition had improved greatly; there was an absence of psychotic symptoms, except for a mild euphoria and disorientation. There persisted for a time a moderate intellectual retardation. No epileptiform seizures were noted after the first few treatments. The ataxia improved greatly. The Wassermann reaction of the blood remained positive, but that of the spinal fluid, which was weakly positive after the fever therapy, became negative at a later date. The colloidal gold curve remained normal throughout the period of observation. In July 1940 he was paroled home. He returned in April 1941 with the statement that although he had gotten along extremely well, making a good home and fairly good occupational adjustment, he had begun to have the epileptiform attacks, usually petit mal, rather frequently. He had been treated by a local physician with dilantin sodium. However, during his absence from the hospital no chemotherapy except some inadequate doses of bismuth subsalicylate had been administered (the family physician failed to administer arsenicals because of poor

veins in the boy's arms). On his return to the hospital he showed a mild nystagmus, a slight internal strabismus and essentially the same improved physical and mental condition as at the time of his parole home. He was immediately given intensive chemotherapy with aldarsone (sodium methylensulfonaminohydroxyphenylarsenate), 1 Gm. intravenously. The petit mal attacks ceased after the second intravenous injection. The nystagmus and strabismus disappeared somewhat later. He left the hospital again in June 1941, with his condition improved and with the assurance that adequate chemotherapy would be given after a rest at home.

CASE 4.—L. B., a 13 year old boy, for four years prior to admission showed a lack of activity and energy, restlessness and an increasing tendency to daydream. About a year prior to admission pupillary changes were noted by the family. There was a history of syphilis in the family. He was admitted to the Hastings State Hospital in August 1940 at the recommendation of the State Child Welfare Association, and the chief observations were a disorientation, a memory defect and, even for a boy of 13, an inadequate grasp of general information. There were a slowing of all psychomotor activity and a decided slurring of speech. He had a shuffling gait, with dragging of the left foot, tremor of the tongue and unequally dilated and sluggish pupils. There was a general hyperactivity of reflexes, and the Hoffmann and the Babinski signs were present. There were a mild ankle clonus and adiadokokinesis. The laboratory examination showed a positive Wassermann reaction of the blood and of the spinal fluid and an increased globulin content and a typical dementia paralytica gold curve of the spinal fluid. He received fifty hours of artificial fever in eighteen weekly sessions, from August to December 1940, together with 0.02 Gm. of mapharsen and 0.1 Gm. of bismuth subsalicylate. In January 1941, on being paroled home, he was much more alert, his intellectual abilities were increased, and he was completely oriented. He had gained weight during the treatments and all neurologic symptoms had improved. The Wassermann reaction of the blood was still positive, but the spinal fluid was normal in every respect. At home he continued to receive adequate chemotherapy. In a check-up in June 1941 it was found that his general psychomotor activity was normal. He was mildly disoriented but only after persistent questioning. The impairment in his speech was now noted only on difficult test phrases. A mild intellectual retardation existed. The pupils were still irregular and sluggish in reaction, and the tendon reflexes were still mildly hyperactive. There had been a consistent gain in weight and the serologic reactions were the same as in January 1941.

CASE 5.—This case is not reported in detail because the patient died during the twelfth fever treatment. An autopsy revealed severe edema of the brain and an overwhelming subarachnoid hemorrhage.

SUMMARY AND CONCLUSIONS

Five patients suffering from juvenile neurosyphilis were treated with artificial fever therapy, produced with the Kettering hypertherm, and with subsequent chemotherapy. One patient died during treatment, and the rest showed physical and mental improvement during an observation period of from one to three and a half years. In 1 instance, a case of

juvenile tabes, the improvement was only of about one year's duration and not great. The serologic reactions of the blood remained positive in all cases. The serologic reactions of the spinal fluid became normal in 3 cases (in 1 of them this improvement was only temporary). One patient, suffering from tabes, showed improvement in the spinal fluid only at the end of two years, after completion of fever therapy.

We recommend the use of this type of fever therapy as a valuable adjunct to the customary chemotherapy in cases of juvenile neurosyphilis and believe that the results compare favorably with those obtained by other investigators with malaria therapy. As in the cases of adult neurosyphilis, the tabetic patient in our series showed no permanent improvement.

SENSITIVITY TO PROTAMINE ZINC INSULIN

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Protamine zinc insulin has been used in treatment in thousands of cases of diabetes mellitus. A survey of the American literature of the past five years reveals but a single report [1] of a case of allergy to this drug. It is this infrequent incidence of sensitivity to protamine zinc insulin that has prompted my presenting the following case.

REPORT OF A CASE

A 56 year old white man presented an itching eruption of the arms, the dorsa of the hands and the palms of one month's duration. The history failed to reveal contact with external irritants. His general health had been good until about three years previously, when his physician discovered that he had mild diabetes mellitus. This condition was controlled by diet alone until about two months before the development of the eruption, when he was required to use 8 units of protamine zinc insulin daily. From the onset of this treatment the patient felt itching and burning and noted redness at the site of each injection, lasting from one to two hours.

Examination of the skin revealed symmetric involvement of the extensor surfaces of the arms with erythematous patches covered by superficial scaling. The dorsa of the hands showed erythematous infiltrated patches, the surface of which was smooth. The palms and palmar surfaces of the fingers showed denuded, shiny, erythematous skin with longitudinal fissures in the creases. A diagnosis of dermatitis medicamentosa due to protamine zinc insulin was made. This was confirmed by an intracutaneous injection of protamine zinc insulin, which produced a decided reaction within three minutes, whereas a control injection of physiologic solution of sodium chloride failed to produce a reaction.

COMMENT

Various possible causes may be suggested for the allergic response to protamine zinc insulin. Which of the components of the drug is the antigen?

Protamine.—According to Kossel,[2] protamines are the simplest of a series of structurally related compounds of which the most complicated are the typical proteins. They are components of fish sperm. In general,

1. Fowler, A. F.; Bensley, E. H., and Rabinowitch, I. M.: Control of Diabetes Mellitus with Protamine Zinc Insulin in Surgery, Canad. M. A. J. **36**:561-568 (June) 1937.

2. Kossel, A.: The Protamines and Histones, translated from the German by W. V. Thorpe, New York, Longmans, Green & Company, 1928.

protamines are excellent precipitants of proteins and with such proteins as insulin form complexes which are sparingly soluble at the p_H of the body fluids. Consequently, on subcutaneous injection of a suspension of this precipitate, a depot is made available, from which insulin is slowly dissolved by the body fluids. The effect exerted by protamine insulin in lowering the blood sugar was found to persist for two to four times as long as that of unmodified insulin. Although many observers have made cutaneous tests with protamine, there have not been any positive reactions. In the group of over a hundred cases reported by Kern and Langner [3] no positive cutaneous reactions were manifested. Thus it appears that protamine is not a sensitizing agent.

Zinc.—Scott [4] showed that insulin could be precipitated in the presence of zinc. Carrying this investigation further, he showed that the addition of small quantities of zinc to protamine insulin caused a prolonged lowering of the blood sugar level which was far more effective than that caused by protamine insulin alone. Batchelor, Fehnel, Thomson and Drinker [5] studied employees who had worked for from two to thirty-five years in a pure zinc industry and observed no acute or chronic illnesses which could be attributed to the metal. They concluded that for years abnormally large amounts of zinc might enter and leave the body without evident damage to health. Absorbed zinc is eliminated from the body in the feces and urine. The quantities of zinc ingested in foods, particularly sea foods, are far greater than the small amounts injected in protamine zinc insulin, and the excretion rate is normally adequate to eliminate several times these amounts through the urine alone. Thus, zinc can be ruled out as a sensitizing agent.

Insulin.—Insulin is a typical protein and is a definite antigen.[6] By diminishing the absorption of an antigen with protamine or other substances which delay the absorption, it is possible occasionally to sensitize a person. For this reason probably more allergic manifestations are noted in patients using protamine zinc insulin than in those using unmodified insulin.[7] Thus it is revealed that allergic manifestations

3. Kern, R. A., and Langner, P. H., Jr.: Protamine and Allergy: Nature of Local Reactions After Protamine Zinc Insulin; Induction of Sensitivity to Insulin by Injections of Protamine Zinc Insulin, J. A. M. A. **113**:198-200 (July 15) 1939.

4. Scott, D. A.: Crystalline Insulin, Biochem. J. **28**:1592-1602, 1934.

5. Batchelor, R. P.; Fehnel, J. W.; Thomson, R. M., and Drinker, K. R.: A Clinical and Laboratory Investigation of the Effect of Metallic Zinc, of Zinc Oxide, and of Zinc Sulfide upon the Health of Workmen, J. Indust. Hyg. & Toxicol. **8**:322-363 (Aug.) 1926.

6. Wasserman, P.; Broh-Kahn, R. H., and Mirsky, I.: The Antigenic Property of Insulin, J. Immunol. **38**:213-219 (March) 1940.

7. Personal communication to the author from the assistant medical director of Eli Lilly & Company, April 1941.

following injections of protamine zinc insulin are due to the insulin itself (when true allergy to insulin itself exists or when delayed absorption of insulin produces sensitization in a person).

Since insulin is specific for the treatment of diabetes mellitus, it must be administered in spite of possible allergic manifestations. In cases in which allergic manifestations arise during the use of protamine zinc insulin, a change to unmodified insulin will remedy the situation unless true allergy to the insulin itself exists. In the latter event, a desensitizing procedure described by Corcoran [8] offers the best solution of the difficulty.

SUMMARY AND CONCLUSIONS

A case of allergic reaction to protamine zinc insulin is reported.

Neither protamine nor zinc is an antigen.

True sensitivity to unmodified insulin is rare.

Sensitization to insulin may occur when its absorption is delayed by the presence of protamine and zinc.

24 Merrimack Street.

8. Corcoran, A. C.: Note on Rapid Desensitization in a Case of Hypersensitiveness to Insulin, Am. J. M. Sc. **196**:359-361 (Sept.) 1938.

ENDOGENOUS ALLERGY

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In contrast with exogenous allergy, the principal causal agents of which are inhaled, ingested, injected or contacted, the term endogenous allergy designates those hypersensitivities in which the allergens are formed within the body. The endogenous allergens may be divided, according to their origin, into two groups: the autoendogenous and the heteroendogenous. One speaks of autoendogenous allergens when autogenous substances (e. g., body cells and their products or tissue fluids) acquire antigenicity under certain conditions, which will be discussed in another part of the paper. Heteroendogenous allergens are foreign substances chiefly of proteinogenic nature which enter the organism from without but which call forth antibody formation only after their multiplication or growth within the body. The chief types of heteroendogenous allergens are bacteria, viruses, fungi and certain parasites, or their products.

For the sake of clarity, it is necessary at the outset to differentiate the endogenous allergens from those agents with which they might possibly be confused. Thus, ingestants (foods or drugs) are often not allergenic in themselves but acquire antigenicity only after transformation by metabolic processes. The resulting substances, in view of their origin, are properly designated as secondary exogenous allergens. Likewise, exogenous partial antigens (exogenous haptens), such as ingested or injected drugs, which become complete allergens only after conjugation with body protein, must also be thought of as exogenous in nature. Finally, in the case of parasites both possibilities exist: They have to be considered as exogenous when acting by inhalation (e. g., Ascaris in laboratory workers) and endogenous when the sensitization occurs after their growth or multiplication within the body.

It is interesting to note that authors in different fields of medicine as early as 1910 tried to explain certain diseases on the basis of an allergy to the body's own protein. Terms such as "autoanaphylaxis" (Elschnig [1]), "autosensitization" (Whitfield [2]), "endoallergy" (von

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1. Elschnig, A.: Studien zur sympathischen Ophthalmie, Arch. f. Ophth. **75**: 459, 1910; **76**:509, 1910; **78**:549, 1911.

2. Whitfield, A.: Some Points in the Aetiology of Skin Diseases, Lancet **2**: 122, 1921; "Auto-Sensitization" in Eczema, Proc. Eighth Internat. Cong. Dermat., Copenhagen, 1930, p. 142.

Bergmann [3]) and "intrinsic asthma" (Rackemann [4]) give some indication of this trend. However, in contrast to the multitude of clinical and experimental studies on exogenous allergy, only a few investigators have worked on the problem of endogenous allergy (Barber,[5] Berger,[6] von Bergmann,[3] Doerr,[7] Duke,[8] Elschnig,[1] Rackemann,[4] Salén,[9] Sulzberger,[10] Urbach [11] and Whitfield [2]). Most of the authors mentioned, however, confined themselves to the rather narrow limits of their specialties, such as the skin, eye, female sexual organs and bacteria. Since no comprehensive survey exists, an attempt is here made to present what I conceive to be the theoretic foundation and clinical manifestations of the endogenously acquired hypersensitivities.

The concept of endogenous allergy is, as will be seen, the logical supplement to the exogenous. It leads one to search not only for allergens coming from without but also for those arising within the body. This knowledge, in turn, has stimulated the development of new diagnostic methods for identifying endogenous allergens, which for obvious reasons cannot be demonstrated by the same technics as used for the exogenous. And, above all, this concept has been instrumental in attempts to work out methods of treatment.

I. AUTOENDOGENOUS ALLERGY

1. *Autoendogenous Allergens.*—Autoendogenous allergens, or, in brief, autoallergens, can arise from many different sources. I shall exclude from consideration those which are physiologic, so to speak, because they do not elicit any morbid reactions. An example would be the type which calls forth the formation of the blood group antibodies. The pathologic autoallergens, on the other hand, consist of altered autogenous proteins which—as a result of autolytic, degenerative or other

3. von Bergmann, G.: Funktionelle Pathologie, Berlin, Julius Springer, 1932.

4. Rackemann, F. M.: Clinical Allergy, New York, The Macmillan Company, 1931.

5. Barber, H. W.: Significance and Pathogenesis of Certain Dermatoses, Practitioner **128**:209, 1932.

6. Berger, W.: Endogene Allergie, Med. Klin. **34**:893 and 989, 1938.

7. Doerr, R.: Allergie und Anaphylaxie, in Kolle, W.; Kraus, R., and Uhlenhuth, P.: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1929, vol. 1, pt. 2, p. 759.

8. Duke, W. W.: Asthma, Hay Fever, Urticaria and Allied Manifestations of Allergy, ed. 2, London, Henry Kimpton, 1927.

9. Salén, E. B.: Spezifisches Allergen aus Menstruationsblut, Acta med. Scandinav., 1934, supp. 59, p. 494.

10. Sulzberger, M. B.: Dermatologic Allergy, Springfield, Ill., Charles C. Thomas, Publisher, 1940.

11. Urbach, E.: Klinik und Therapie der allergischen Krankheiten, Vienna, W. Maudrich, 1935.

physicochemical processes—have become foreign to the organism and have thus acquired antigenicity. More specifically, autoallergens are derived from the breakdown or the catabolic products of diseased organs, particularly the skin, endocrine glands and liver; from intermediary or split metabolic products, and, finally, from the disintegration of tissue fluids (exudates and transudates) and hemorrhages.

Autogenous allergens may be subdivided, as are the exogenous allergens, into primary and secondary ones and possibly also into haptens.

The primary allergens are those which originate directly from diseased tissues or abnormal endocrine products. As an example of how a diseased organ can give rise to autogenous allergy, one may cite sympathetic ophthalmia. It has been established by immunologic methods that this condition represents an allergic response to the patient's own uveal pigment. In addition, there is evidence that abnormal endocrine products may cause allergic manifestations, as demonstrated serologically by antihormones.

Secondary autoendogenous allergens are conceivably formed in the following manner: When a tissue is sensitized, whether by exogenous or endogenous allergens, and its protein as a result of a severe reaction is rendered foreign to the organism, this altered protein may act as a new allergen on other organs. This is demonstrated clinically by the appearance of a different type of manifestation in a different organ after a suitable incubation period. The following case may clarify this concept.

A woman 21 years of age and in good health, who had never previously received any type of serum, was given a prophylactic injection of diphtheria toxin-antitoxin. Forty-eight hours later the site of injection (the upper part of the thigh) presented a severe local reaction with diffuse and brawny swelling (Arthus phenomenon). This persisted for six days and was followed by pain in several joints. On the tenth day after the injection an urticarial exanthem appeared on the posterior aspects of the arms, and there was also a simultaneous flare-up of the reaction at the site of injection. Nine days later the urticarial outbreak increased in intensity and spread to the face, neck, back and lower extremities. Four days later the former urticaria was replaced by an acute vesicular dermatitis (fig. 1), although no local therapy had been used.

In view of the fact that the second urticarial rash occurred just nine days after the first one, the condition may be properly classified as a fractionated serum sickness. The eczematous rash, however, I consider to be an expression of an allergy to a secondary endogenous allergen. The latter arose from the "heterogenization" [12] of cutaneous proteins as a result of the severe local anaphylaxis (Arthus phenomenon). This conclusion is further supported by the fact that eczematous lesions have never been observed in serum sickness, since the shock organ is the blood

12. By heterogenization is meant such alteration of body protein that it becomes foreign (heterogenous) to the organism.

vessels and not the epidermis. Hence the dermatitis may be best explained on the basis of an endoallergy caused by a secondary endogenous allergen. To analyze this case further, it is apparent that the horse serum in the antitoxin is a primary exogenous allergen, producing the fractionated serum sickness. It is not the horse serum, however, but the body proteins altered by the severe Arthus phenomenon which presumably allergized the epidermis, producing a dermatitis.

Fig. 1.—Vesicular dermatitis as a manifestation of endogenous allergy.

The concept of an endogenous allergy caused by secondary endogenous allergens was first formulated on an experimental basis by Manwaring and his associates [13] and clinically by Barber.[5] The latter assumed that certain bacteria, by acting on a previously allergized

13. Manwaring, W. H., and others: Relation of Anaphylaxis to Immunity: Phenomenon of Antiphylatoxic Immunity, J. Immunol. **13**:63, 1927; Relation of Anaphylaxis to Immunity: Normal and Anaphylactic Detoxication of Specific Foreign Proteins, ibid. **13**:357, 1927.

organ, such as the liver, so alter some of the liver protein that it becomes allergenic and must be considered a secondary endoallergen. Barber stated the belief that the appearance of urinary proteoses in such cases was evidence of a secondary endogenous allergen. He tried to explain the clinical observation that different allergens may elicit the same allergic symptoms in a person on the basis of this mechanism.

In addition to the primary and secondary endogenous allergens, it is conceivable that diseased or altered tissue substances may assume the character of haptens. This means that autogenous substances acquire the capacity of reacting specifically with appropriate antibodies but lack the ability to call forth the production of antibodies. I should like to advance the hypothesis that endogenous lipids and carbohydrates may under certain circumstances act in this way. This view would be analogous to the well known fact that lipids and carbohydrates when introduced into the body may act as exogenous haptens and become complete antigens on conjugation with proteins. The same concept may apply even more to heteroendogenous allergy, with particular reference to bacteria. On the basis of the investigations of Heidelberger and Avery and of others, it seems likely that the carbohydrate and lipid constituents rather than the proteins of bacteria are responsible for allergization. Sensitization to autogenous lipids has been demonstrated by Henning.[14]

I fully appreciate the fact that this concept, as attractive as it may be on clinical grounds, must remain hypothetic so long as the secondary endogenous allergens cannot be isolated in order to demonstrate an antigen-antibody reaction. It will be readily understood that the antibodies produced by these autoallergens cannot be demonstrated by the usual methods. Occasionally it is possible to find the endoallergen in the patient's urine in the form of Oriel's proteose. Rarely the antigen is to be found in the blood, for example, in certain menstrual allergies (Géber and Urbach), in the menstrual discharge (Salén) or in the milk (Duke).

If, however, future experimental work will confirm the idea of an endogenous allergy due to secondary as well as primary allergens and endogenous haptens, it will serve to explain a host of hitherto vague symptoms which possess some of the characteristics of hypersensitiveness but which have never been shown to be due to exogenous allergens.

2. *Clinical Manifestations of Autoendogenous Allergy.*—A. Due to Blood and Blood Serum as Autoendogenous Allergens: The classic

14. Henning, L.: Gelingt es bei Meerschweinchen mit Gemischen aus alkoholischen Extracten arteigener Organe und Schweineserum positive Seroreaktionen, sowie anaphylaktische Lipoid-Antikörper zu erzeugen? Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:19, 1928.

proof of the existence of autoallergens—and, incidentally, the most thoroughly investigated example—is paroxysmal hemoglobinuria. This term describes the clinical syndrome in which, after exposure to cold, there appear chills, fever and a transitory hemoglobinuria, accompanied by manifestations of the nature of Widal's hemoclastic crisis (drop in blood pressure and in leukocyte count, change in the refractometric index of the serum, change in the coagulability of the blood, etc.). Donath and Landsteiner [15] have shown that a true antigen-antibody reaction is the cause of these manifestations and that antibodies (autohemolysins) directed against the body's erythrocytes have been produced within the organism. Miyakava experimentally demonstrated the appearance of antibodies following the destruction of erythrocytes in the blood stream by means of phenylhydrazine.

Autoagglutination might also be included here. This is observed in a great variety of diseases, including cirrhosis of the liver, hemolytic icterus, leukemia, malaria, syphilis and carcinoma. Further investigation will be necessary to determine whether or not one may include here intragroup agglutination (immune isoagglutination) following repeated blood transfusions. As the term indicates, this condition represents sensitization of the red blood cells to blood of its own group (for further details see Levine and Stetson [16] and Mosonyi [17]).

Whitfield drew attention to the fact that deep-seated ecchymosis, such as that due to trauma, fractures or torn muscles, was followed within nine to twelve days by generalized erythematourticarial eruptions. Similar observations have been made by Barber and others, including myself (fig. 2). Particularly interesting is the occasional occurrence of urticarial zones surrounding hemorrhagic purpuric lesions, as noted by Whitfield; presumably these are due to a local autoallergic mechanism.

It must be noted, however, that both human beings and animals can become hypersensitive not only to the erythrocytes of their own blood but also to their own serum or plasma. Bizzozero has demonstrated that repeated intracutaneous injections of their own serum sensitized the skin of 9 of the 25 persons on whom the experiment was performed. Comparable to this are the reports of Nelli, Netter, Nathan and Grundmann, Marie, Tezner and Reiter, who have described the

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15. Donath, J., and Landsteiner, K.: Ueber paroxysmale Hämoglobinurie, Ztschr. f. klin. Med. **58**:173, 1905.

16. Levine, P., and Stetson, R. E.: An Unusual Case of Intragroup Agglutination, J. A. M. A. **113**:126 (July 8) 1939.

17. Mosonyi, L.: Intra-Group Agglutination, J. A. M. A. **113**:1349 (Sept. 30) 1939.

18. Footnote deleted on proof.

19. Footnote deleted on proof.

appearance of serum sickness following injections of homologous serum in persons who had previously received human serum. Schmidt [20] even reported a case of death in protracted shock following the second subcutaneous injection of measles convalescent serum eight days after the first.

Eickhoff, as well as Geissendörfer, duplicated these observations in animals. Autogenous serum repeatedly administered parenterally was capable of eliciting allergic reactions almost identical with those from foreign serums.

Fig. 2.—Diffuse urticaria appearing ten days after a severe abrasion of the skin over the sternum.

B. Due to Exudates and Transudates as Autoendogenous Allergens: This group of manifestations of endogenous allergy is comprised of those due to absorption of autogenous protein which has become, in effect, foreign to the body. Duke,[8] for example, published a report of 3 women who had a serum-sickness-like symptom complex following rapid absorption of their own milk. In each case the condition could be relieved through the use of the breast pump. In 1 instance, in which the condition followed the weaning of a baby, the symptoms were so severe that it was

20. Schmidt, H.: Referat über die geweblichen Äusserungen der Allergie, Verhandl. d. deutsch. path. Gesellsch. **30**:36, 1937.

necessary to administer epinephrine repeatedly. In 1 of the patients, who had been secreting about 1 drachm of milk a day during the seven years following the weaning of her child, passive transfer was successful only with her own milk and not with cow's milk. Furthermore, injection of 0.02 cc. of a 1:10,000 solution of her own milk was followed not only by a most severe urticarial reaction but also by an attack of asthma and an intense general pruritus. Subsequent to these reactions, the patient became insensitive to her own milk, and the secretion of milk decreased, stopping altogether after about three weeks.

Falls, Freda and Cohen [21] observed that nonpregnant women of the child-bearing ages give a positive immediate reaction to the intracutaneous administration of 0.01 cc. of colostrum, while pregnant women do not. The authors concluded that the body is allergized to the protein by the small amount of colostrum produced after puberty in the breasts of nonpregnant women. Pregnancy, by gradually increasing the colostrum production, creates a temporary specific anergy for this protein. A similar mechanism of specific anergy resulting in a cutaneous insensitiveness to fetal protein in gravid women will be discussed in the section on allergy to pregnancy.

Rapid absorption of pleural or peritoneal exudates or of synovial effusions following aspiration of a joint has occasionally been observed to bring on serum-sickness-like conditions (such as urticaria, angioneurotic edema, hydroarthrosis and fever). In this connection, mention should also be made of the urticarias following vaccination (fig. 3), burns and prolonged exposure to sunlight. I might also include here the allergic reactions which have been observed following injections of autogenous exudates.

C. Due to Proteoses Excreted in the Urine (Oriel's proteose): There is extensive literature on the question whether the proteoses found by Barber and Oriel [22] in the urine in allergic diseases are specific endogenous allergens. Here I should like to consider only the following questions: Is this substance excreted in greater quantity during allergic attacks? Is it specific? Does it have any therapeutic value?

None of these queries has, as yet, been satisfactorily answered, despite the fact that numerous reports of investigations on urinary proteoses have appeared in the past ten years. Many authors, including Tuft and Brodsky, Villalba and Urbach, have confirmed the observation

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21. Falls, F. H.; Freda, V. C., and Cohen, H. H.: A Skin Test for the Diagnosis of Pregnancy, Tr. Am. A. Obstetricans, Gynecologists & Abd. Surgeons **53**:62, 1940.

22. Barber, H. W., and Oriel, G. H.: Clinical and Bio-Chemical Study of Allergy, Lancet **2**:1009 and 1064, 1928. Oriel, G. H.: Further Observations on the Biochemistry of Asthmatic Conditions, with Special Reference to Urinary "Proteose," Lancet **2**:406, 1933.

that larger amounts of proteose are excreted during allergic attacks than during the free intervals. The specificity of the proteoses, however, is emphatically disputed by Freeman, Cormia, Cornbleet and many others; while Burgess, who checked Oriel's observations at the request of the British Medical Association, as well as van Leeuwen, R. Barany, Kallós, Black, Shelmire and Gaté, confirmed Oriel's observations. Gaté reported the interesting observation that the proteose produces specific reactions only when injected together with the serum of the same person. Regarding therapeutic results with this substance, Trasoff and Meranze,

Fig. 3—Erythematourticarial eruption occurring eight days after the height of a severe vaccinal reaction.

Vaughan, Tuft and Brodsky and many others had no success. On the other hand, Liebman and Bigland, Darly and Whitehead, Eichenlaub, Gaté, Burgess and others reported some good results.

How are these widely divergent opinions to be explained? On the basis of my own investigations, I venture the following conclusion: It is chiefly in cases of endogenous allergy that allergens (primary or secondary) are likely to be excreted in the urine in such a state that they can be utilized for testing or therapy; in cases of exogenous allergy the allergens generally will have been so altered or destroyed that their derivatives in the urine will have lost their antigenicity. Furthermore,

I believe that the technic of Thiers [23] should always be employed for the extraction of the proteoses. Together with Gaté, I should like to warn against the use of strong concentrations for testing purposes; such concentrations may act nonspecifically and may occasionally elicit severe focal and general reactions. I recommend that the first injection should not exceed a concentration of 1:10,000.

I am of the opinion that in cases of endogenous allergy therapeutic trial with autogenous urinary proteoses is warranted. Figure 4 shows an angioneurotic edema of unknown origin. This condition could be evoked by administering autogenous urinary proteoses. After ten injections the patient became asymptomatic, apparently as a result of the treatment.

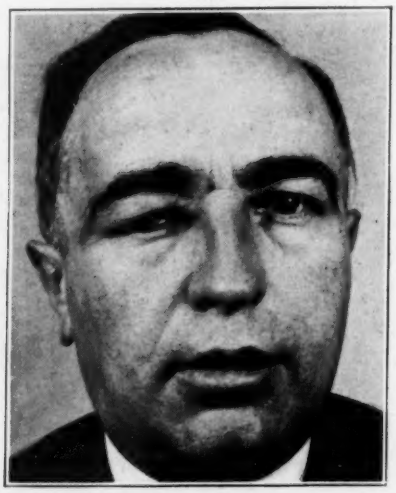

Fig. 4.—Angioneurotic edema, clinical recurrence of which could be elicited by injections of autogenous urinary proteoses.

A similar mechanism may perhaps be the basis of the good results obtained by Jausion and Pagès [24] with autourotherapy in light dermatoses.

D. Due to Diseased Tissues as Autoendogenous Allergens: While only relatively few observations can be cited to illustrate the action of altered tissue protein as endogenous allergens, it is my conviction that this mechanism is operative far more often than can be actually demonstrated in the present state of knowledge.

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23. Thiers, H.: Technique modifiée d'extraction de la proteóse d'Oriel, Bull. Soc. franç. de dermat. et syph. **40**:1233, 1933.

24. Jausion, H., and Pagès, F.: Les maladies de lumière et leur traitement, Paris, Masson & Cie, 1933.

(1) Altered tissues of the eye as endogenous allergens: Long before the term endogenous allergy was coined, certain diseases of the eye were considered as clinical expressions of autoanaphylaxis. As early as 1910 Elschnig [1] assumed that the cause of sympathetic ophthalmia was a sensitization to the organ-specific uveal pigment, which as a result of trauma to the uvea had been destroyed and absorbed. The pigment was assumed to induce the formation of organ-specific antibodies with consequent sensitization of the remaining uveal structures and of the opposite eye. Woods [25] supported this hypothesis by demonstrating that patients with sympathetic ophthalmia usually give positive cutaneous reactions to uveal pigment, while control subjects give no reactions. On the basis of these studies, he employed uveal pigment as a therapeutic agent in the treatment of this disease and reported good results.

According to Verhoeff and Lemoine,[26] hypersensitiveness to lens protein may be considered as the possible cause of endophthalmitis phacoanaphylactica. After an operation on the lens of the eye lens substance is liberated, and this material brings on a phacoanaphylactic inflammation which prevents complete healing after cataract extraction. Courtney [27] reported that a patient with this condition gives positive cutaneous reactions to lens protein. Burky [28] demonstrated that in rabbits which had been allergized to a lens toxin combination typical endophthalmitis developed after the injection of lens protein into the anterior chamber of the eye. Burky and Woods [29] utilized this knowledge for prophylactic and therapeutic purposes. They observed that desensitization with lens proteins in patients who gave positive reactions to lens extracts before operation tended to ameliorate or even totally inhibit such postoperative inflammation.

Furthermore, certain forms of keratitis parenchymatosa are said to be of endoallergic origin. Both Löw and Frieberg described cases of such a condition occurring postoperatively. These cases were instances of keratoplasty in which extremely severe noninfectious parenchymatous inflammation of the cornea set in ten to fourteen days after the operation. It was assumed that the patient had been allergized by absorption of corneal protein released in the course of the first operation and that the

25. Woods, A. C.: Allergy and Immunity in Ophthalmology, Baltimore, Johns Hopkins Press, 1933.

26. Verhoeff, F. H., and Lemoine, A. N.: Hypersensitiveness to Lens Protein: Patient Desensitized and Successfully Operated on for Immature Cataract, Am. J. Ophth. **5**:700, 1922.

27. Courtney, R. H.: Use of Lens Protein Tests Before Cataract Operations, Am. J. Ophth. **12**:20, 1929.

28. Burky, E. L.: The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of Staphylococcus Toxin, J. Allergy **5**:466, 1934.

29. Burky, E. L., and Woods, A. C.: Lens Protein, Arch. Ophth. **57**:41, 1928.

second operation (keratoplasty, iridectomy) had elicited allergic inflammation of the cornea. Löwenstein [30] expressed the opinion that the keratitis parenchymatosa which appears in the course of trachomatous processes of long duration is to be attributed to absorption of altered corneal protein as a result of local nutritional disturbances.

(2) Altered cutaneous protein as an endogenous allergen: Not only blood serum but tissue fluid may act as an endogenous allergen. Thus, Whitfield [2] reported a case of acute vesicular eczema in which the serous discharge, trickling over the normal skin of the patient, produced a fine vesicular eruption, while the patient's serum did not produce any reaction on his own skin. From this observation the author concluded that a human being may become allergic to the products of his own broken-down tissues. On the basis of a number of such clinical observations Whitfield claimed that the generalized papulovesicular eruptions sometimes seen to follow severe scratching and/or irritating therapy of a localized patch of chronic eczema are attributable to hypersensitiveness to tissue products which have become foreign to the body. The same holds true for disseminate rashes which may sometimes follow irritating local treatment of varicose ulcers or severe scratching of an eczema on the lower part of the leg (based on circulatory disturbances, etc.).[31] Whitfield called this phenomenon autosensitization.

(3) Other altered organ proteins as endogenous allergens: While the two preceding sections dealt with protein of the eye and of the skin respectively, because there is some detailed knowledge, the present discussion will include observations relating to the most varied organs. The reason so little is known about the internal organs as sources of endogenous allergens is that the evidence can be only indirect, consisting of clinical observations. Thus, disappearance of cutaneous or other allergic manifestations following the surgical removal of a diseased organ may or may not be convincing proof of an endoallergic mechanism. Furthermore, methods of antibody determination are possible only in those few instances in which the endogenous allergens can be isolated. Thus, Read, Heilbrunn and Liebert [32] employed complement fixation methods to demonstrate that after insulin shock therapy in persons with schizophrenia the brain tissue is altered, as evidenced by the presence of circulating antibodies specific for the white matter of the brain.

The following examples, however, strongly suggest the possibility of this hypothesis. In a case of resistant urticaria, a hydatiform mole was

30. Löwenstein, A.: Die allergischen Erkrankungen des Auges, in Fortschritte der Allergielehre, Basel, S. Karger, 1938.

31. Brown, W. H.: Some Clinical Manifestations of Endogenous Sensitization Eruptions Following Local Infection or Injury, Brit. J. Dermat. **51**:197, 1939.

32. Read, C. F.; Heilbrunn, G., and Liebert, E.: Studies in Insulin Treatment of Dementia Praecox, J. Nerv. & Ment. Dis. **90**:747, 1939.

ultimately discovered, and its removal was promptly followed by complete cure. Figure 5 shows an urticarial exanthem in a patient 70 years of age with a carcinoma of the rectum. This disappeared after extirpation of the neoplasm.

Barber [5] and von Bergmann [3] expressed the opinion that hepatic diseases particularly may lead to the production of endogenous allergens.

I realize, of course, that clinical results in cases of this kind do not prove that the resorbed material acted as an allergen and not as a toxin.

Fig. 5.—Generalized urticarial exanthem of three months' duration in a patient 70 years of age with carcinoma of the rectum. After extirpation of the neoplasm the rash disappeared.

Future investigation involving cutaneous tests with the suspected tissue protein as well as confirmation by antigen-antibody reactions will be necessary before the conditions in such cases may be properly classified as endogenous allergies.

E. Hormonal Endogenous Allergy: Even with the present limited knowledge, the endocrine hormones would seem to act as endogenous allergens frequently. This can occur either during functional alterations

or as the result of actual pathologic changes in the endocrine glands. As such functional changes as menstruation and pregnancy far outnumber diseases of the endocrine system, allergic manifestations are much more often observed in the first group. Hence it is possible to consider them in some detail, while other hormonal allergies can receive only brief discussion.

(1) Estrogens as endogenous allergens: Allergic manifestations associated with menstruation, ovulation and pregnancy comprise such varied clinical pictures as migraine, asthma, acne and certain forms of eczema. The first question to be considered is of course whether or not these conditions are of autotoxic or endoallergic origin. This can best be answered by examining separately the conditions in menstruation and pregnancy.

Menstrual allergy. Géber [33] must be given credit for first demonstrating, by experimental methods, that there is some substance circulating in the blood stream when menstrual urticaria appears. He was able to show that urticarial attacks can be provoked during the intermenstruum by intravenous injections of blood serum taken from the patient during the premenstrual flare of the cutaneous lesions; the same serum elicited no reactions in controls. These observations were confirmed by Lichter [34] and Harrison.[35] Géber [36] contributed an even more important discovery: that the disturbances incident to menstruation can be cured by systematic injections of the blood serum taken during the exacerbation of the cutaneous lesions, asthma or other symptoms.

Similar favorable therapeutic results were reported—independently, in part, from those of Géber—by Hopkins and Kesten,[37] Malinin,[38] Harrison [35] and Salén.[9] The last author employed menstrual discharge collected during the first hours of menstruation, before it becomes definitely sanguineous. For therapy, Géber recommended the intracutaneous administration of 0.2 to 0.4 cc. of serum (preserved with 0.3 per cent phenol) every other day. The injections are to be carried out

33. Géber, J.: Einige Daten zur Pathologie der Urticaria menstruationalis, Dermat. Ztschr. **32**:143, 1921; Desensitization in the Treatment of Menstrual Intoxication and Other Allergic Symptoms, Brit. J. Dermat. **51**:265, 1939.

34. Lichter, A.: Experimentelle Urtikaria hervorgerufen mit Krankenserum eines Falles von Urticaria menstrualis, Dermat. Wchnschr. **79**:847, 1924.

35. Harrison, W. T.: Case of Menstrual Allergy, J. A. M. A. **100**:738 (March 11) 1933.

36. Géber, H.: Desensibilisationsversuche bei Menstruationsintoxikationen, Med. Klin. **31**:1203, 1935.

37. Hopkins, J. G., and Kesten, B. M.: Urticaria: Etiologic Observations, Arch. Dermat. & Syph. **29**:358 (March) 1934.

38. Malinin, A. J.: Ueber Menotoxikosen und ihre Behandlung mit Eigenblut, Dermat. Wchnschr. **83**:1881, 1926.

according to the depot method of Lehner and Rajka: four injections into the same cutaneous site.

Urbach [39] reported a case of dermatitis dysmenorrhoeica which appeared three to four days before each menstrual period (fig. 6), and at this time a substance was found in the patient's blood which elicited severe immediate as well as delayed reactions when injected into her skin (fig. 7). No reactions were observed in controls. When an intervening pregnancy interrupted ovarian activity, there was an almost complete remission of objective signs and subjective symptoms.

In 2 cases of eczema seen by me, in which the eruption was localized on the hands and forearms and definitely flared up before each menstrual

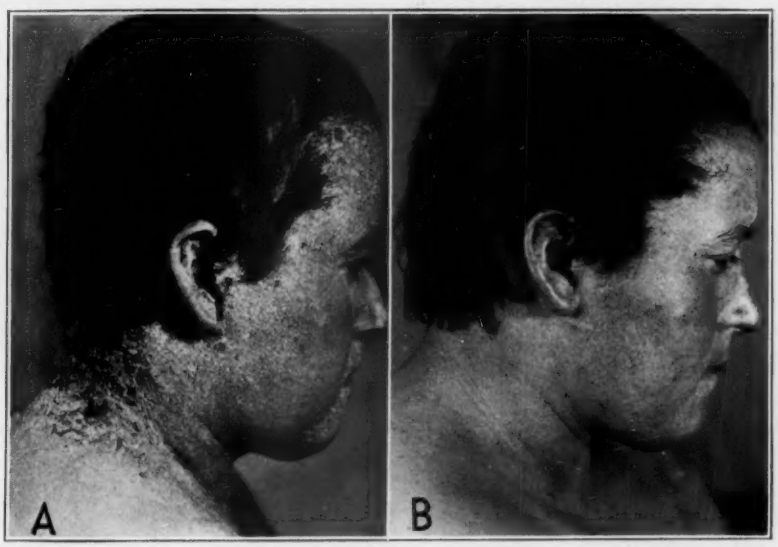

Fig. 6.—Dermatitis dysmenorrhoeica with flare-up (*A*) before and during the menstrual period. There was complete remission of the condition (*B*) following temporary roentgen ray castration.

period, the cutaneous condition yielded readily to intracutaneous injections of autoserum withdrawn during the height of the eruption. I employed the same method in the treatment of some 20 patients with acne menstrualis. This condition is characterized by a definite flare-up of the lesions prior to or during the menstrual period (fig. 8). Cameron [40] reported good therapeutic results with autogenous premenstrual serum in menstrual migraine.

39. Urbach, E.: Menstruation Allergy or Menstruation Toxicosis Including a Contribution to the Specific Treatment of Menstrual Acne, Internat. Clin. **2:** 160, 1939.

40. Cameron, J. M.: An Autogenous Serum for the Treatment of Menstrual Migraine, Pennsylvania M. J. **43:**709, 1940.

Fig. 7.—Demonstration of endogenous allergen (in this case a "meno-allergen") by cutaneous tests (same patient as in figure 6). *M*, positive reaction to autogenous premenstrual serum. *NM*, negative reaction to premenstrual serum of a control. *N*, negative reaction to autogenous intermenstrual serum. *G*, negative reaction to serum of a pregnant woman.

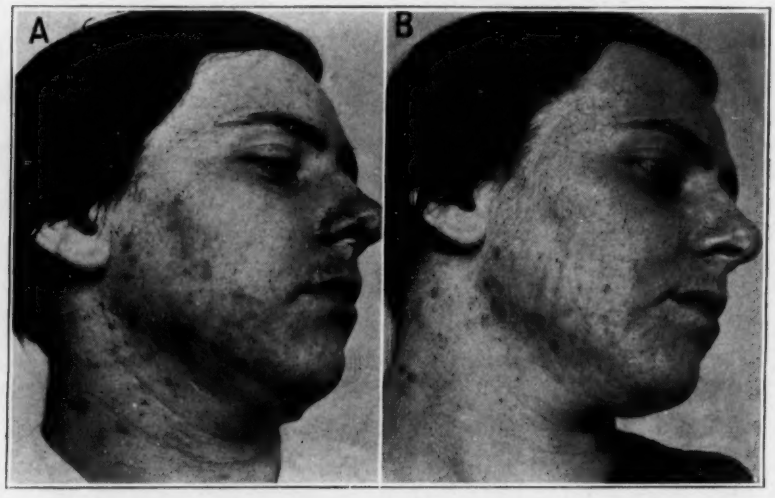

Fig. 8.—Acne vulgaris with exacerbation (*A*) two to four days before each period. Definite improvement (*B*) following two courses of intracutaneous injections of autoserum (no local treatment) during the intermenstrual period.

It might seem simple to decide the question of allergy versus toxicosis by testing the patient intracutaneously with her own premenstrual serum or with menstrual secretion. The decision would be in favor of the toxin theory if both the patient and the controls reacted to the intradermal injection of premenstrual blood serum during the intermenstruum. But the evidence would favor the assumption of an endogenous allergen if only the patient—and not the controls—reacted. This distinction holds in cases in which the skin represents the shock organ, as in dermatitis dysmenorrhoeica and menstrual eczema. However, in other forms of menstrual allergies in which the shock organ is not the skin (e. g., menstrual asthma and migraine), a negative reaction to a cutaneous test does not rule out the existence of a menstrual allergen. Although both possibilities must be granted in principle, the present state of knowledge makes it difficult to determine whether one is dealing with a hormonal endogenous allergy on the basis of an antigen-antibody reaction or with a nonallergic hypersensitiveness (pathergy) to a toxic substance (such as a menotoxin). I am conducting antihormone determinations in an attempt to differentiate between menstrual allergy and toxicosis.

In my opinion, the following facts favor the idea of an allergy:

1. In cases of menstrual urticaria attacks were provoked during the intermenstruum by injection of premenstrual serum (Géber, Lichter and Salén).

2. In dermatitis dysmenorrhoeica and menstrual eczema local reactions were induced with premenstrual blood only in the patients themselves and never in other women (Urbach).

3. In several cases of menstrual asthma it was possible to perform passive transfer of the hypersensitiveness to menstrual secretion (Salén [41]).

4. A woman who had had an anaphylactic shock following an injection of estrone (theelin) thereafter regularly had the same syndrome (urticaria, sneezing and asthma) shortly before each menstrual period (Waldbott [42]).

As regards the source of the menstrual allergen, Géber stated the opinion that it is produced by disturbances in the endocrine functions of the ovaries. Salén, on the other hand, expressed the belief that the endogenous allergens originate from the endometrium broken down during the menstrual cycle.

In this connection, it might be pertinent to mention those rare cases of acne and eczema which I observed in which the conditions manifested themselves at the time of the rupture of the Graafian follicle. The

41. Salén, E.: Arbeten från Sabbatsbergs Sjukhus, 1935.

42. Waldbott, G. L., in discussion on Criep, L. H.: Allergy to Pancreatic Tissue Extract, J. Allergy **12**:165, 1941.

patients responded readily to appropriate endocrine therapy. Here, too, one may consider the possibility of ovarian substances acting as endogenous allergens.

Allergy due to pregnancy. As early as 1908 Rosenau and Anderson demonstrated that guinea pigs can be allergized to extracts of guinea pig placenta. These authors suggested the possibility of autosensitization and based an explanation of eclampsia on these experiments.

During recent years attempts have been made to interpret the so-called toxemias of pregnancy as allergic in nature. The fetus, as well as the placenta, was considered to act as the endogenous allergen. This theory was based, in part, on the fact that during pregnancy the organism—and especially the skin—shows a definite hypersensitiveness to substances originating in the fetus and also to placental protein. The serum of pregnant women possesses proteolytic capacity for placental protein; furthermore, after injection of this protein it is possible to demonstrate specific antibodies in the blood of pregnant women. Yamada [42a] found that the isolated uterine musculature of guinea pigs sensitized to eclamptic serum is thrown into acute anaphylactic tetanus on the addition of 0.2 Gm. of eclamptic placental proteins.

Another example of the altered reactivity of the gravid organism, this time due to an endogenous hapten, may be found in the following observations: Pregnant women give decidedly weaker reactions to intracutaneous injections of extracts of organs than do nonpregnant women and men; but, as the extensive studies of Gans [43] have shown, addition of serum from pregnant women to the injected organ extract reverses the results: that is, the organ extract plus this serum brings on far stronger local reactions in pregnant than in nonpregnant women. It seems, therefore, that serum from pregnant women contains a substance to which the pregnant organism is hypersensitive. This substance might be considered an endogenous hapten, since the serum alone is not capable of eliciting these cutaneous reactions. This view conforms with Jegorow's observation that only pregnant women give cutaneous reactions to split products of placental protein obtained by a special "lysate" method.

Starting from the hypothesis that the fetal protein may act in the maternal organism as an allergen against which antibodies are formed, I [44] injected fetal extract intracutaneously in a series of patients. Normal women and those in the first few months of pregnancy gave strong papuloerythematous reactions in twenty-four hours, while preg-

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42a. Yamada, K. I.: Effect of Visible Light on Biologic Reaction of Eclamptic Blood Serum and Eclamptic Placenta, Jap. J. Obst. & Gynec. **23**:141 (June) 1940.

43. Gans, O.: Ueber unspezifische Reaktionen der menschlichen Haut, Dermat. Wchnschr. **73**:841, 1921.

44. Urbach, E., in discussion on Herrmann, E., and Schiller, W.: Zur Geschlechtsspezifität der Haut, Klin. Wchnschr. **6**:925, 1927.

nant women in the final trimester gave negative or only slightly positive reactions. These results can be explained only on the basis that the gravid organism eventually acquires a specific anergy to the fetal proteins. It is interesting to note how similar this mechanism is to that of the cutaneous sensitiveness of gravid women to colostrum.

Mention should also be made here of the good results obtained in the treatment of dermatoses of pregnancy with systematic injections of the serum of normal pregnant women. The results of this therapeutic measure may be explained by the fact that the blood of these patients contains an abnormal number of endogenous allergens which are neutralized by the antibodies in the administered serum.

According to Finch,[45] the nausea and vomiting accompanying pregnancy are due to the patient's hypersensitiveness to the secretion of her own corpus luteum of pregnancy. Finch claimed that his hypothesis is proved by the following facts: 1. Pregnant women suffering from this syndrome give strong immediate cutaneous reactions to 0.02 cc. of progestin. 2. Several of the pregnant patients who gave 3 or 4 plus reactions to progestin intradermally subsequently (as late as five weeks after the injection) reported that whenever they became severely nauseated the site of injection flared with a wheal and erythema accompanied by itching. 3. The patient's symptoms could be alleviated or completely controlled by the injection of graduated doses of progestin.

(2) Other hormones as endogenous allergens: Numerous reports testify that persons have been proved to be sensitive to such endocrine products as insulin, pituitary, thyroid and pancreatin. The present discussion is confined to experimentally confirmed observations of cases in which the patient was hypersensitive to the endocrine product itself and not to the animal protein from which it was derived or to the diluent in which it was dissolved (such as corn oil and peanut oil). Harten and Walzer[46] have recently reviewed this topic thoroughly.

It was Tuft[47] who first brought forth unequivocal proof of specific hypersensitiveness to endocrine products. He established the existence of allergic hypersensitiveness to insulin by means of cutaneous tests and by demonstrating the presence of specific circulating Prausnitz-Küstner antibodies to this substance. These observations were confirmed with respect to insulin allergy by Sammis[48] and Lasch[49] and with respect to hypersensitiveness to solution of posterior pituitary by Simon and

45. Finch, J. W.: Etiology of Nausea and Vomiting of Pregnancy, J. A. M. A. **111**:1368 (Oct. 8) 1938.

46. Harten, M., and Walzer, M.: Allergy to Insulin, Liver, Pituitary, Pancreas, Estrogens, Enzymes, and Similar Substances, J. Allergy **12**:72, 1940.

47. Tuft, L.: Insulin Hypersensitiveness, Am. J. M. Sc. **176**:707, 1928.

48. Sammis, F. E.: Hypersensitiveness to Insulin, J. Allergy **6**:387, 1935.

49. Lasch, F.: Ueber Insulinanaphylaxie, Med. Klin. **31**:975, 1935.

Ryder.[50] It should be pointed out that endogenous allergies due to endocrine products can sometimes be manifested as a hyposensitiveness or insensitiveness. Thus, insulin resistance, apart from that associated with endocrine or hepatic disease, severe infections, etc., may be taken as an example of refractoriness to endocrine principles.

In the study of autogenous organ-specific allergization, special significance must be attributed to the antihormones. This term is applied by Collip to substances which appear in the serum of animals undergoing long periods of treatment with anterior pituitary or other endocrine substances. These antihormones apparently explain the observed loss of responsiveness to such extracts, and they are also capable of making other animals, previously untreated, refractory to these substances. It should be pointed out that antihormones, unlike other antibodies, reduce the specific sensitiveness of an organism. However, the question as to whether the antihormones are immune bodies has not been settled. A full discussion will be found in the recent paper of Thomson, Collip and Selye.[51]

Another important fact in connection with endogenous allergy to hormones is that antihormones such as antithyrotropic substance have been detected in the serum of normal untreated animals of various species as well as of normal human beings. Furthermore, antihormones have been produced by injecting sheep pituitary extract into sheep or by implanting pituitary glands of rats into rats. If it is possible to sensitize human beings and animals to autogenous hormones (as demonstrated by the appearance of antihormones), it would seem obvious that pathologically altered endocrine organs could all the more readily produce substances to which the organism might become hypersensitive. I have observed cases of urticaria in which the condition did not yield to therapy until a concurrent thyroid disturbance (such as toxic goiter and thyrotoxicosis provoked by iodine) was eliminated. In this connection the research of J. T. King on neurocirculatory asthenia is interesting in that he showed the condition to be characterized frequently by a great sensitiveness to the injection of epinephrine. By injecting this substance, he reported, the characteristic symptoms of the disorder were reproduced; hence, "It is likely that men suffering from this condition are sensitive to their own adrenalin." Sulzberger [10] extended the scope of this concept when he wrote:

> If human beings and animals can become sensitized to organ-specific factors when these are administered from without, cannot the organ-specific factors which

50. Simon, F. A., and Ryder, C. F.: Hypersensitiveness to Pituitary Extracts, J. A. M. A. **106**:512 (Feb. 15) 1936.

51. Thomson, D. L.; Collip, J. B., and Selye, H.: The Antihormones, J. A. M. A. **116**:132 (Jan. 11) 1941.

the organs themselves are producing within the individual also, on occasion, be liberated and slightly altered and thus produce autogenous organ-specific sensitization? Is it not possible that these sensitivities to specific substances derived from the human pancreas, the human liver, etc., all within the human being, may give rise to organ-specific antibodies which may then be able, on occasion, to attack the specific organ-substances in vivo and to damage the particular organ in situ?

Definite confirmation of the present attempts to demonstrate the existence of hypersensitiveness to organ-specific autogenous products might yield unexpected results. Certain conditions which are suggestive of allergy (especially those presenting the clinical pictures of urticaria, angioneurotic edema and eczemas and also, in certain cases, vasomotor rhinitis and migraine) but in which it has been impossible to prove an underlying allergic mechanism may eventually be explained on this ground.

F. Physical Allergies: Recent experimental and immune biologic investigations permit the assumption that at least some of the patients with so-called physical allergies are sensitive to a modified form of their own protein. In other words, the action of physical agents (such as cold, heat and pressure) so alters the body's protein (generally of the skin) that it acquires antigenicity and becomes an endogenous allergen.

Karady [52] has recently reported a series of animal experiments which if duly confirmed may serve to clarify the pathogenesis of physical allergies. The importance of these studies seems to warrant their description:

1. Guinea pig serum was exposed to cold (— 5 C.) or to heat (56 C.) for one and one-half minutes and was then injected into a group of normal guinea pigs. Three weeks later reinjection of similarly treated serum caused an anaphylactic shock, but only when the serum used had been exposed to the same physical condition.

2. Exposure of guinea pigs' hindlegs to cold (— 5 C.) or to heat (56 C.) followed in three weeks by injection of serum exposed to cold or to heat resulted in anaphylactic shock in the correspondingly treated group but not in the cross-treated group.

3. Similar exposure of the guinea pigs' hindlimbs followed by reexposure after three weeks also resulted in anaphylactic shock. Cross experiments again gave negative results.

In this connection, Burky's ingenious experiments [28] are of interest. Rats can be allergized to extract of rat muscle when mixed with staphylococcus toxin. These animals thereby become hypersensitive not

52. Karady, S.: Rôle of "Auto-Antigens" in the Pathogenesis of Physical Allergy, J. Immunol. **37**:457, 1939.

only to rat muscle but to trauma as well, probably because substances are liberated in the tissues identical with those in the extract of rat muscle.

The experiments of Karady are based on the assumption that the exposure of the organism to physical forces might lead to chemical-structural changes in the protein of the plasma or cells and that these changes might suffice to bring about denaturization of the protein of the organism, thus transforming it in effect into a protein foreign to that organism. The denatured protein so produced might act as an allergen and might thus lead to antibody formation.

This new evidence does not, of course, indicate that the same mechanism is the basis of all conditions belonging to the group of physical allergy. As outlined by my co-authors and me,[53] physical hypersensitiveness may be due to a pathergic response; i. e., there is no specific antigen-antibody mechanism involved. Roth and Horton [54] have shown that the symptoms in such cases are probably elicited by the release of histamine from the cells, as a direct result of the trauma. Of course, further investigation may possibly unite both concepts on an allergic basis, if an endogenous allergen can be demonstrated in all such cases.

Aside from these animal experiments, several clinical immunologic studies seem to suggest the probability of an endogenous origin in some instances of physical allergies. Sézary, Horowitz and Rivoire [55] reported the case of a patient who after exertion suffered from an urticarial-hemorrhagic exanthem as well as from pains in the joints. These symptoms could be elicited experimentally by means of intravenous injections of a proteose extracted from the patient's urine. Furthermore, several authors reported that they were able to effect passive transfer of hypersensitiveness to physical agents, such as cold and heat (Harris, Lewis and Vaughan, Lehner and Rajka, Liebner, Prieto and others). The reason so few successful passive transfer observations have been described is undoubtedly that it is so difficult to isolate the endogenous allergen involved. However, this problem can perhaps be solved, as Melczer and Wlassics [56] have shown, by using the tissue antibodies contained in blister fluid (Urbach-Königstein method). If the usual

53. Urbach, E.; Herrman, M. F., and Gottlieb, P. M.: Cold Allergy and Cold Pathergy, Arch. Dermat. & Syph. **43**:366 (Feb.) 1941.

54. Roth, G. M., and Horton, B. T.: Histaminase in Hypersensitiveness to Cold, J. A. M. A. **110**:686 (Feb. 26) 1938.

55. Sézary, A.; Horowitz, A., and Rivoire: Purpura rhumatoïde anaphylactique à poussées subintrantes provoquées par l'effort musculaire, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:760, 1931.

56. Melczer, M., and Wlassics, T.: Ueber die Wärmeüberempfindlichkeit, Arch. f. Dermat. u. Syph. **176**:157, 1937.

procedure fails, I recommend the so-called reverse technic, in which the endogenous allergen is first produced locally by exposing an area of skin of a normal subject to cold, heat or pressure. Then the tissue antibodies contained in the fluid from a blister raised by a cantharides plaster on the skin of the patient allergic to the specific physical agent are injected. A positive reaction is manifested by a large wheal.

II. HETEROENDOGENOUS ALLERGY

1. *Heteroendogenous Allergens.*—This group comprises, as previously mentioned, the allergens which arise within the body but which are not derived from the body's own substances. The chief representatives of this category are infectious and parasitic agents.

2. *Clinical Manifestations of Heterogenous Allergy.*—A. Due to Infectious Agents: One of the oldest facts in allergy is that such organisms as bacteria, viruses and fungi are able to allergize their host, that is, to induce the formation of specific antibodies. The extent to which the disease symptoms in infectious and parasitic allergies are based on this mechanism is still unsettled. This decision is especially difficult because the infectious antigens have the capacity of multiplying and also because they are often primary cytotoxic agents. In dealing with these antigens, therefore, one encounters situations that are far more complex and far more obscure than in allergic conditions due to primarily harmless proteins which are incapable of multiplying.

Furthermore, it is conceivable that the infectious agents themselves do not act as antigens, but rather intermediary products which result from the action of the bacteria on body protein.

Infectious agents can become active as antigens in the following three ways:

1. They can enter into the organism from without, multiply there, induce antibody formation and thus elicit allergic reactions. This is the case in all acute infectious diseases. It was von Pirquet [57] who first called attention to the fact that many of the clinical observations in acute infectious diseases correspond with the symptoms seen in serum sickness and experimental anaphylaxis. He referred to such clinical observations as the incubation period of some eight to ten days followed by an exanthem, the regularity of the course and the recurrence of manifestations in stages. According to von Pirquet, the incubation period is not the time during which the agents multiply but rather the time necessary for the formation of antibodies to the bacterial protein. But even in diseases with a short term of incubation, allergy cannot be ruled out on this basis alone. It must be borne in mind that this can occur espe-

57. von Pirquet, C.: Allergie, München. med. Wchnschr. **53**:1457, 1906.

cially in diseases due to ubiquitous agents; in these cases allergization may have taken place previously.

2. Infectious agents may not begin their allergizing influence until they have existed within the organism for some time. This is generally the case in chronic infectious diseases (such as tuberculosis and syphilis) as well as in focal infection. Allergic phenomena in chronic infectious diseases are well known. Thus, the phases of immunity alternating with evident signs of disease are definite indications of an altered reactivity. This has been appreciated for a long time in the cutaneous manifestations of tuberculosis or tertiary syphilis with their characteristic peripheral extension and central healing. The tuberculoid structure is the histologic expression of a bacterial-allergic origin. Focal infections play an especially important role in bacterial allergization. Extensive clinical experience has convincingly shown that these foci are capable of primarily causing and/or maintaining a state of hypersensitiveness. This is the underlying mechanism in many cases of chronic asthma (the "intrinsic asthma" of Rackemann) and in some cases chronic urticaria and chronic eczema, as well as in certain rheumatoid diseases and arthritides.

3. Infectious agents can bring on allergic phenomena by means of endogenous reinfection. When bacteria, fungi and viruses reach allergized skin from remote sites by way of the blood, disease phenomena follow which are known as ids. These include the tuberculids, trichophytids, syphilids and levurids. This opinion is substantiated by the observation of living organisms in the blood and tissues, provided examination is done at the proper time, i. e., shortly before the generalized eruption appears. It may be reemphasized that a highly sensitized tissue is a prerequisite, as proved by the strong cutaneous reactions to such substances as tuberculin and trichophytin. Furthermore, Whitfield and Barber called attention to disseminated allergic cutaneous eruptions in association with impetiginous streptococcic infections of the skin or subcutaneous tissue and proposed the term streptococcids. Similar clinical pictures are occasionally observed in patients with boils, carbuncles or abscesses. Here the evidence points strongly to a similar allergic mechanism with the staphylococcus as the bacterial antigen causing the generalized eruption (fig. 9).

B. Due to Parasites: It is a well established fact that parasites such as echinococci, tapeworms, round worms and trichinas are able to allergize their host (Casoni, Botteri, W. Jadassohn, Fülleborn, Morenas, Rackemann and Stevens and others).

However, which of the symptoms in naturally occurring infestations may be regarded as allergic? Some of the pathologic manifestations

may be attributed to the purely physical and nonallergic effect of the parasites (cyst of an echinococcus in the lung or of a cysticercus in the brain). Other clinical manifestations are certainly due to primarily toxic substances produced by some parasites.

Fig. 9.—Disseminated vesicular dermatitis (left thigh, leg and forearm) occurring about ten days after the onset of impetigo in the region of the knee and probably due to resorption of altered cutaneous protein. The dermatitis healed without treatment in a few days.

On the other hand, the endogenous-allergic mechanism may be operative in those cases of asthma, rhinopathy, conjunctivitis, intestinal "colic," pruritus, urticaria and angioneurotic edema in which the patients are worm infested. The allergic origin is dramatically demonstrated

when, for example, a typical anaphylactic shock (with or without asthma) follows the rupture of an echinococcic cyst in the course of an operation.

To what extent allergy is responsible for the eosinophilia accompanying many infestations is still unknown.

SUMMARY

Endogenous allergy, in contrast to exogenous allergy, embraces those types of hypersensitiveness and hyposensitiveness which result from allergens formed within the body itself. The endogenous allergens may be divided according to their source into two groups: the autoendogenous and the heteroendogenous. The autoendogenous allergens arise from altered endogenous substances as a result of autolytic, degenerative or other changes in the tissues. The heteroendogenous allergens are derived from heterogenous protein, chiefly of bacteria, fungi, parasites, etc., after sufficient multiplication or growth within the body.

In the present state of knowledge, the following disease entities may be included in the category of autoendogenous allergy: paroxysmal hemoglobinuria, autoagglutination, syndromes resembling serum sickness from absorption of autogenous protein (such as milk, hematomas, exudates and degenerated tissues), cutaneous autosensitization phenomena, autoanaphylactic ocular diseases, menstrual allergy, allergy due to pregnancy, other hormonal allergies and certain physical allergies.

The heteroendogenous allergies can give rise to equally varied manifestations, both in acute and in chronic infections and infestations. The former group includes certain acute exanthems and some acute arthritides. Examples of chronic infectious allergies, including those due to focal infections, are the so-called infectious asthmas, some chronic urticarias, some chronic eczemas, the id phenomena of the skin and certain rheumatoid diseases.

The concept of endogenous allergy will undoubtedly advance knowledge of the etiology, diagnosis and therapy of allergic diseases.

Recognition of the fact that autogenous substances, micro-organisms and parasites may act as endogenous allergens will induce the physician to search for them in cases in which no exogenous allergen can be found even after prolonged and elaborate investigation.

New diagnostic methods are of course necessary for the identification of these endogenous allergens. Such methods include the use of uveal pigment, human milk, menstrual serum, urinary proteoses and undenatured bacterial antigens as test substances, as well as the determination of antihormones.

Finally, it has been shown that application of these principles is of definite therapeutic value in dealing with a number of allergies of endogenous origin.

XANTHOMA DIABETICORUM WITH UNUSUAL FORM OF ERUPTION

REPORT OF A CASE

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AND
JOHN GARB, M.D.
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The eruption herein described occurred in a Negress suffering from diabetes. The clinical features of the eruption are so unusual that their description is deemed to be worthy of publication.

REPORT OF CASE

History.—Mrs. L. C.,[1] a Negress aged 34, was admitted to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital for treatment on May 28, 1940, with cutaneous lesions of four years' duration. Her mother died of diabetic gangrene. At the age of 16 years the patient had "painful swollen knees" for six months. She had been known to have diabetes for eight years. Her usual diet consisted of fattening foods, so that she became obese. Five years ago she "began to reduce." She lost some weight and became nervous and weak. A year later yellowish spots appeared suddenly on the extensor surfaces of the arms, a week or two later on the feet and legs and within a month on the rest of the body. These attacks of showers of papules and nodules were usually immediately preceded by sensations of burning and heat and were followed by frontal and occipital headaches. She also complained of polyuria, polydipsia, nocturia and pain in the right hypochondrium radiating to the back at the level of the ninth dorsal vertebra. Within two years keloid-like growths developed, at first discrete but later fused to form bizarre figures. The lesions on the body annoyed her only slightly because of the slight itching and the disfigurement; but the growths on the palms, fingers and soles, because of involvement of the tendons and the interphalangeal joints, caused considerable pain and discomfort, forcing her to hold her fingers in a semiflexed position.

Dermatologic Examination.—The eruption was symmetric and consisted of pinhead-sized to match head–sized round yellowish brown hard shiny papules and nodules, isolated and discrete, grouped and confluent, forming variously sized irregular, linear and stellate patches. They were located mostly on the extensor surfaces and sides of the upper and lower extremities, including the palms and soles, but were less abundant on the back and nates. There were also numerous papules on the roof of the mouth and under the finger nails and toe nails.

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

1. The patient was presented before the New York Dermatological Society, Oct. 22, 1940 (Wise, F.: Xanthoma Diabeticorum, Arch. Dermat. & Syph. **43**:1043 [June] 1941).

The scars of vaccination and of wounds due to removal of tissue for biopsy and the scars on the forehead were free of any growths. On the left elbow and on the extensor surfaces of the arms, forearms and knees were linear growths varying from 2 to 4 inches (5 to 10 cm.) in length, some raised to ⅛ inch (0.4 cm.) and so shaped that they formed bizarre rhomboid-like designs, with ramifications projecting from the ends and sides, resembling the twigs of a tree. These growths were of a keloid-like hardness and infiltrated the entire skin but moved freely with it. They had yellowish summits with light brown bases and dark brown halos about ¼ inch (0.6 cm.) in width. After three months of antidiabetic regimen and thyroid medication the halos vanished and the keloid-like growths became

Fig. 1.—Keloid-like growths on the extensor surfaces of the right elbow, arm and forearm (*A*) and of the left elbow (*B*) with unusual bizarre rhomboid-like designs.

uniform in color and much softer. The patient was able to extend the hands completely and in general felt much better.

General Physical and Special Examinations.—The patient was 5 feet 4½ inches (164 cm.) in height, weighed 165 pounds (75 Kg.) and appeared to be in good health. The pupils were equal, round and regular, were about 3 mm. in width and reacted well to light and in accommodation. The fundi, throat and larynx were also normal except that the tonsils were infected. The thyroid was not enlarged. The lungs were clear. The heart was of the transverse type with no chamber enlargements, and sounds were of good quality. There were no murmurs.

The pulmonic second sound was equal to the aortic second sound when the patient was upright and greater than the aortic second sound when she was supine. The aorta was normal. The blood pressure was 168 systolic and 118 diastolic in the left arm and 170 systolic and 114 diastolic in the right arm. The electrocardiogram showed "a low T wave in leads 1 and 2 and slight left axis devia-

Fig. 2.—*A*, symmetric unusual configuration on the extensor surfaces of the knees (the lesions are not the result of scratching, as the patient had only slight itching and did not scratch). *B*, involution of the lesions on May 26, 1941, though the improvement was as great on Aug. 28, 1940, three months after treatment by antidiabetic diet and administration of thyroid.

tion but otherwise no evidence of cardiac involvement." The edge of the liver was not palpable. Gynecologic examination disclosed perineal and cervical lacerations. The uterus was normal in size and freely movable. The report of the roentgenogram of the skull was as follows: "The sella turcica is within the normal 10 per cent limits. The posterior clinoid process is large with a small vacuole at its base. There is otherwise no pressure atrophy here or elsewhere discernible."

Laboratory Data.—The Wassermann reaction was negative, and the result of a Kline precipitation test was normal. The hemogram showed 10,700 leukocytes

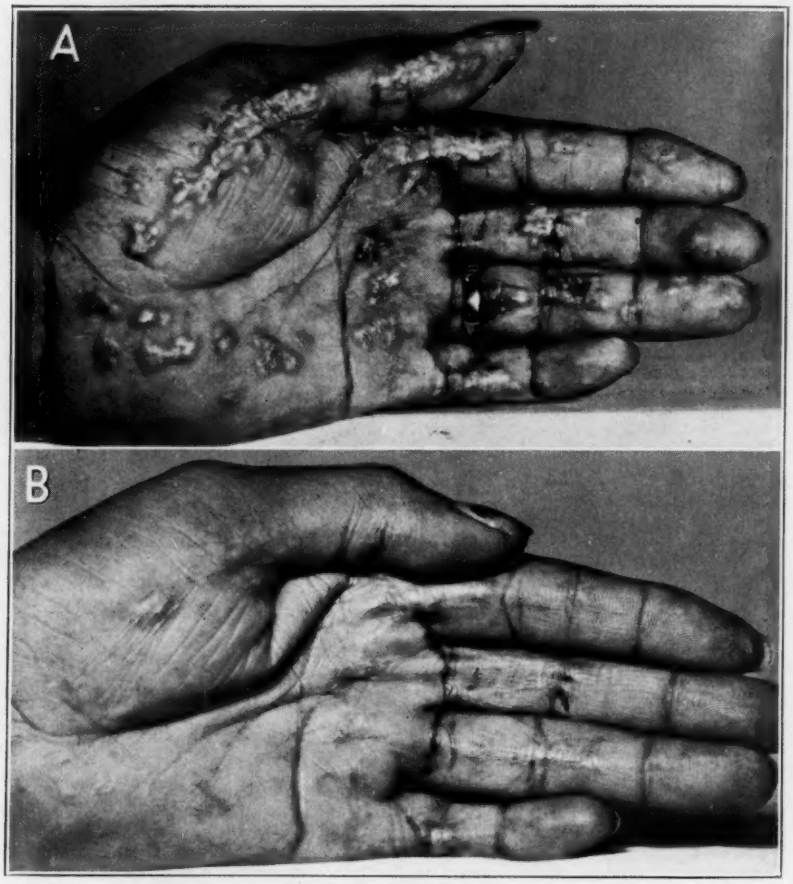

Fig. 3.—*A,* numerous nodules on the creases of the palms and on the tendons. The patient was unable to flex or extend the hands. *B,* regression of the lesions (photograph taken May 26, 1941). This regression was noticed Aug. 28, 1940, three months after treatment by antidiabetic diet and thyroid medication.

and 4,300,000 erythrocytes per cubic millimeter and a normal hemoglobin content and differential count. A twenty-four hour specimen of urine was examined on May 28, 1940, with the following results: volume 920 cc., reaction acid, specific gravity 1.037, albumin 0.46 Gm., sugar 2.5 per cent and phosphorus 1.8 Gm. as phosphorus pentoxide (normal 2.5 to 3 Gm. per twenty-four hours), a few epithelial

cells and numerous casts. Bacteriologic examination of the urine showed alpha streptococci, over 200 colonies per cubic centimeter, and no tubercle bacilli. There was only a faint trace of sugar in the urine on March 27, 1941.

TABLE 1.—*Chemical Observations on the Blood: Partition of Lipids According to the Method of Bloor*

Date	Specimen Examined	Constituents *	Amount per 100 Cc.
May 31, 1940	Whole blood (blood very lipemic)	Urea nitrogen (10-15 mg.)	10.5 mg.
		Uric acid (2-4 mg.)	3.1 mg.
		Chlorides, as sodium chloride (450-500 mg.)	380 mg.
		Dextrose (60-100 mg.)	250 mg.
		Cholesterol, total (160-230 mg.)	820 mg.
June 14, 1940	Serum	Cholesterol	
		Total (160-230 mg.)	1,045 mg.
		Esters (100-150 mg.)	612 mg.
		Ratio of esters to total (40 to 60 per cent)	59 per cent
Oct. 14, 1940	Serum	Proteins	
		Total (6-8 Gm.)	7.2 Gm.
		Albumin (4-5 Gm.)	3.1 Gm.
		Globulin (2-3 Gm.)	4.1 Gm.
		Ratio (1.6 to 2.1)	0.76 per cent
		Lipids, total (500-700 mg.)	2,539.4 mg.
		Fatty acids (200-420 mg.)	1,852.0 mg.
		Lipid phosphorus (7-14 mg.)	16.1 mg.
		Cholesterol	
		Total (160-230 mg.)	675 mg.
		Esters (100-150 mg.)	485 mg.
		Ratio of esters to total (40 to 60 per cent)	72 per cent
March 4, 1941	Whole blood	Urea nitrogen (10-15 mg.)	12 mg.
		Dextrose (60-100 mg.)	130 mg.
	Serum	Lipids, total (500-700 mg.)	1,096 mg.
		Fatty acids (200-420 mg.)	633 mg.
		Cholesterol (160-230 mg.)	450 mg.
March 25, 1941	Whole blood	Dextrose (60-100 mg.)	110 mg.
	Serum	Cholesterol	
		Total (160-230 mg.)	750 mg.
		Esters (100-150 mg.)	490 mg.
		Ratio of esters to total (40 to 60 per cent)	65 per cent

* Figures in parentheses indicate normal range (per hundred cubic centimeters).

TABLE 2.—*Chemical Observations on the Bile (Oct. 19, 1940)*

Bile	Cholesterol, per 100 Cc.	Bile Salts, per 100 Cc.	
		Aldrich-Bledsoe	Reinhold-Wilson
Before stimulation (duodenal drainage)	Negative *	200 mg. (300-400 mg.)†	Negative
After stimulation with magnesium sulfate (1 oz. given in glass of water ten minutes before drainage)	270 mg. (150-200 mg.)	1,260 mg. (800-1,200 mg.)	1,000 mg.*
After stimulation with olive oil (1 oz. given ten minutes before drainage)	Negative (oil interference)	1,260 mg. (800-1,200 mg.)	1,250 mg.

* Normal result.
† Figures in parentheses indicate normal range.

Course.—The following observations were noted on the patient's history chart:

"Oct. 8, 1940: The patient has been taking thyroid regularly but not following the diet.

"Nov. 28, 1940: There are new lesions appearing on the hands and fingers because the patient has not been discreet in her diet.

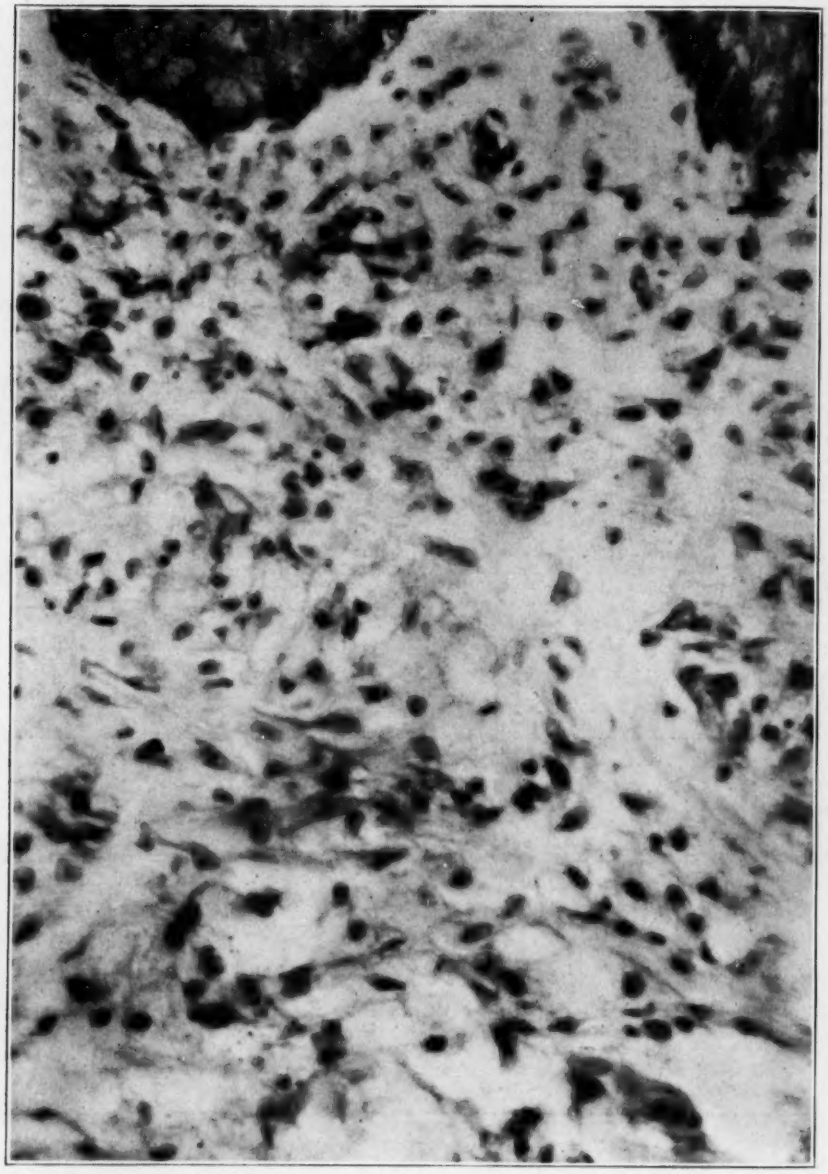

Fig. 4.—Photomicrograph of keloid-like tissue on the arm showing numerous xanthoma cells (× 375).

"May 15, 1941: The patient has been taking insulin once a day since Feb. 26, 1941. She has not been observing her diet, especially with regard to cholesterol intake."

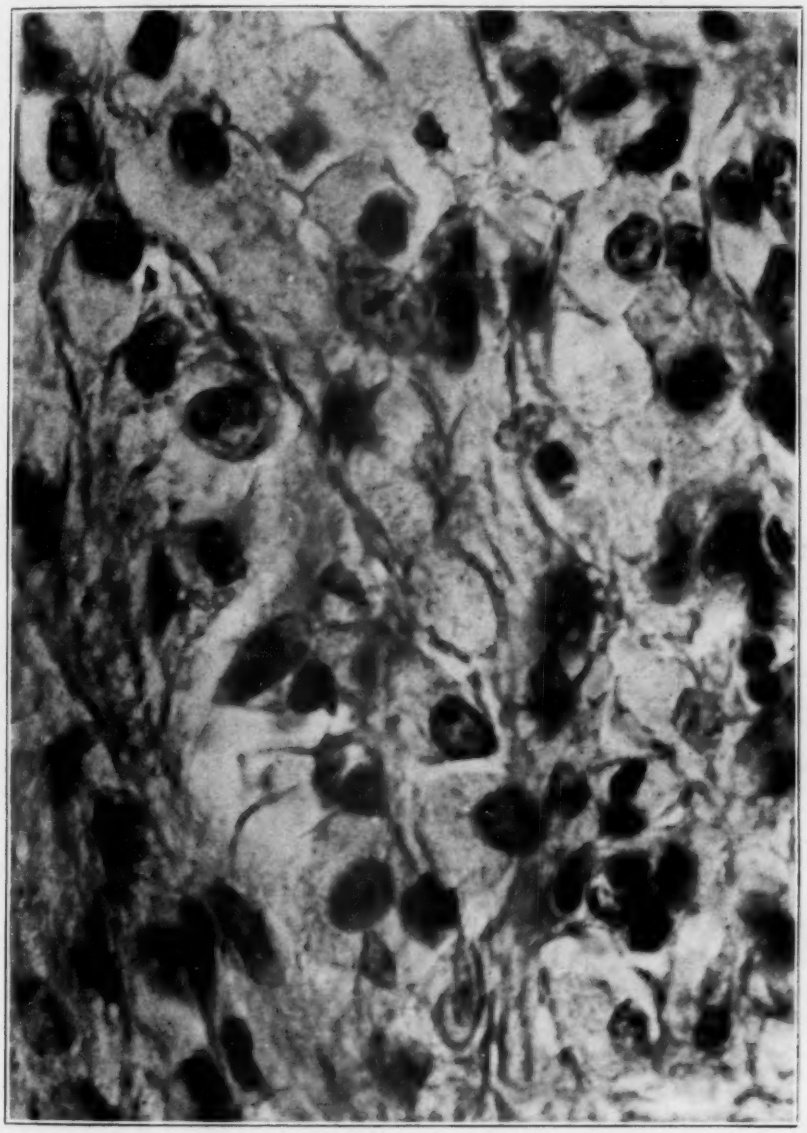

Fig. 5.—High power photomicrograph of the same lesion as in figure 4 (× 850).

Histologic Observations.—A keloid-like nodule, 1.5 cm. in diameter, was excised for chemical examination of the tissue with regard to lipid contents, but it was found to consist mostly of fibrous tissue, the quantity of xanthomatous tissue

being insufficient for a lipid partition. The tissue was then subjected to histologic study by Dr. Wilbert Sachs, who made the following observations:

Low Power Magnification: "Throughout the middle and upper parts of the cutis there is a large mass composed chiefly of cellular elements. At the edge of the section there is a pronounced increase in fibrous tissue between these cellular masses. The overlying epidermis is irregularly acanthotic, and the basal cell margin is intact and contains considerable pigment. The horny layer is increased and densely laminated. There are no other important changes within the epidermis."

High Power Magnification: "The cells composing the mass are large and have large round fairly well stained vesicular nuclei. The cytoplasm is foamy, and the cell outline is clearly seen. Throughout the increased fibrous area there is a diffuse infiltration of fibroblasts. The entire picture is that of a xanthoma, and the microscopic structure at the edge could well fit in with keloid changes."

COMMENT

History and Physical Examination.—The sudden eruption of the lesions, the presence of glycosuria and of the inflammatory areola around the nodules, the complete resolution of the lesions on the skin, tendons and mucous membrane of the roof of the mouth with even a softening and partial involution of the keloid-like growths and the disappearance of the halo paralleling the reduction in the hyperlipemia as a result of an antidiabetic regimen and thyroid medication are outstanding characteristics of xanthoma diabeticorum.

The xanthoma planum on the skin and tendons of the palms and fingers and the papulopustular type of eruption in this patient are more commonly a manifestation of tuberous xanthomatosis and are frequently associated with xanthomatous biliary cirrhosis. On the other hand, the patient did not have jaundice, severe itching or enlarged liver and spleen, which are the main features of the latter syndrome. No evidence of disease of the gallbladder could be found either by physical or by laboratory examinations except in the history of pain referable to the ninth dorsal vertebra. The icterus index could not be determined because it was "too lipemic to read."

Lesions were conspicuously absent in the scars due to vaccination and to the removal of tissue for biopsy and in the scar on the forehead. Weidman and Boston [2] have emphasized the usual occurrence of xanthomatous deposits in cicatricial tissue.

The bizarre appearance of the lesions and the unusual configurative design were not due to trauma, as the patient did not complain of itching and did not scratch. The nodules on the extensor surfaces of

2. Weidman, F. D., and Boston, L. N.: Generalized Xanthoma Tuberosum with Xanthomatous Changes in Fresh Scars of Intercurrent Herpes Zoster: Adenocarcinoma of the Ampulla of Vater at Necropsy, Arch. Int. Med. **59**:793 (May) 1937; abstracted, Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1937, p. 156.

the elbows and knees looked like typical keloid growths and cords but microscopically were found to consist mostly of fibrous tissue and xanthoma cells.

Laboratory Data.—The laboratory data show a reversal of the albumin-globulin ratio in the serum (0.76 on Oct. 14, 1940, table 1), a small amount of urine (920 cc.), a high specific gravity (1.037), moderate albuminuria (0.46 Gm. of albumin) and the presence of hyperlipemia and hypercholesteremia. These observations together with the absence of signs of cardiac hypertrophy, of retinal changes and of renal insufficiency resemble the general symptoms of lipoid nephrosis of a mild type, not sufficient to produce the symptoms of edema. These data might also fit in with chronic diffuse nephritis observed in association with diabetes mellitus, in which disease some of the manifestations correspond to those of chronic nephrosis [3] while others are referable to inflammatory changes in the kidneys. Some evidence of mild renal changes is indicated by the diminution of the urinary phosphate to 1.8 Gm. as phosphorus pentoxide in a twenty-four hour specimen.

On Oct. 14, 1940 there was a rise of total cholesterol esters to 72 per cent. This was followed by the appearance of new lesions and aggravation of the general condition. It occurred in spite of the lowering of the total cholesterol content (1,045 mg. per hundred cubic centimeters on June 14, 1940 and 675 mg. on October 14). This is a clear demonstration that the metabolic disturbance does not depend so much on the accumulation of a particular lipid as on the relative concentration of the various lipid constituents, especially the ratio of the cholesterol esters to the total cholesterol. It tends to confirm the theory advanced by Schaaf [4] as to the pathogenesis of xanthomas. He stated that as long as there are no qualitative changes in the lipid ratio, quantitative changes of the individual lipids may occur without causing any damage. This has been experimentally proved with Ringer's solution containing proteins in amounts corresponding to those in blood serum. It was found that the optimal distribution of neutral fat in the presence of cholesterol and cholesterol esters took place only if the cholesterol esters constituted 60 per cent of the total cholesterol. This was again clearly expressed by Schaaf in the following statement:

> Abnormal ratio between emulsifying agents in the presence of a normal total lipoid content or total cholesterol content leads to labile fat-emulsion, to facilitated deposition of fat and thus to xanthomas; or normal adaptation of emulsifying agents in the presence of an increased lipoid content leads to stabile emulsion and no deposition of fat, and thus to absence of xanthomas.

3. Kahn, N., in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1921, vol. 2, p. 275.

4. Schaaf, F.: On the Experimental Production of Xanthomas in Laboratory Animals, J. Invest. Dermat. **1**:11-30 (Feb.) 1938.

Histopathologic Changes.—In his discussion of the pathologic changes of xanthoma diabeticorum Crocker [5] stated:

> The diseased process appears to be anatomically of the same nature as ordinary nodular xanthoma but with more inflammatory phenomena and less connective tissue growth. . . . Large cells with several nodules are found in this as in the other form and they seem to be in abundance in proportion to the size of the lesions. As might be anticipated from the clinical features, the predominance of active inflammatory changes is the most important and striking difference between the two forms.

Ormsby [6] also stated:

> Histologically, there is close resemblance between this disorder and xanthoma multiplex, but in this variety there are more likely to be accompanying signs of inflammation. The xanthoma-cells . . . are fewer in number, and in the later stages there is less connective-tissue formation.

Thannhauser [7] stressed repeatedly in his book on lipidoses that

> Only a few scattered foam cells may be detected in the inflammatory tissue in the eruptive nodular form of xanthoma. . . . In secondary xanthoma the inflammatory reaction is prevalent and foam cells are detected only after the careful search in sections of the lesions.

The histologic sections of nodular lesions taken from different areas from our patient show numerous foam cells. Dr. Thannhauser studied our slide and gave the following report:

> After examining the slide I should like to say that the xanthoma cells do not run in layers or in nests surrounded by granulomatous tissue. There is quite a bit of inflammatory reaction but no giant cells (Touton cells). . . . The amount of foam cells dispersed in a tissue which shows inflammatory reaction is unusually great for secondary xanthomas. However, I should not hesitate to say that according to the slide (without knowing the history in the case) the condition is an eruptive form of xanthomatosis due to hyperlipemia with inflammatory reaction. I admit that the differentiation of tuberous xanthomatosis and the eruptive form of xanthomatosis due to hyperlipemia may cause in such instances as this some difference of opinion in the evaluation of the histologic picture. However, I think histologic differentiation is also possible in this case.

Treatment.—An antidiabetic diet and 3 grains (0.2 Gm.) of thyroid daily were prescribed for our patient by Dr. King. Within three months there was a complete resolution of the papulopustular lesions and even a decided regression of the keloid-like growths took place. Later, when the patient began to neglect her diet, the eruption recurred. On Jan.

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5. Crocker, H. R.: Diseases of the Skin, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1903, p. 752.

6. Ormsby, O. S.: Diseases of the Skin, ed. 4, Philadelphia, Lea & Febiger, 1934, p. 667.

7. Thannhauser, S. J.: Lipidoses: Diseases of the Cellular Lipid Metabolism, New York, Oxford University Press, 1940, pp. 68 and 108.

28, 1941 a low fat and low animal cholesterol diet was prescribed (to which the patient adhered), together with subcutaneous injections, 10 units daily, of protamine zinc insulin. Within three weeks the growths again regressed. The patient was carefully watched for possible symptoms of vitamin A deficiency (especially with reference to night blindness), which may be a complicating factor in persons given a regimen low in fat or cholesterol.

SUMMARY

An unusual form of eruption of xanthoma diabeticorum is described, with keloid-like growths on the extensor surfaces and sides of the upper and lower extremities. The lesions were absent in scars.

The eruption in this patient had the features of both the nodular type of secondary xanthomas complicating diabetes and the papulopustular eruption occurring in patients with xanthomatous biliary cirrhosis or extracellular cholesterosis (Thannhauser).

There was a recurrence of xanthomatous lesions following an abuse of the diet by the patient. This coincided with a rise in the cholesterol ester ratio from 60 to 72 per cent. It would bear out the theory of Schaaf that the formation of xanthoma depends on the ratio of the esters to total cholesterol (60 per cent is normal). In that percentage the lipids form the finest and most stable emulsion.

There were many foam cells in the nodules, which is contrary to the usual sparsity of these cells in secondary xanthomas.

Miss Doris E. Richey and Miss Eleanor Engs, of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, did the photographic work in this study.

816 Fifth Avenue.

219 East Nineteenth Street.

ADENOMA OF SEBACEOUS GLANDS (ADENOMA SEBACEUM)

WITH CONSIDERATION OF KERATOTIC ADENOMA SEBACEUM AND TRUE ADENOMA OF SEBACEOUS GLANDS

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PITTSBURGH
AND
S. WILLIAM BECKER, M.D.
CHICAGO

Just as there is considerable difference of opinion relative to the criteria for diagnosis of benign neoplasia of various glandular structures throughout the body, so some confusion exists in the evaluation of benign neoplastic growths of the sebaceous glands of the skin. A benign neoplasm of a glandular structure is called an adenoma. In a discussion of this designation, Ewing [1] stated:

> When one considers the great variety of conditions, in which an adenomatous morphology is presented, and analyzes their physiological and clinical significance, the conclusion must be reached that adenoma is rarely a distinct morphological entity, but is rather to be regarded as a series of structures which tissues assume in response to various forms of irritation, functional activity, and overgrowth.

Beck [2] emphasized the differences of opinion relative to classification of abnormal growths originating in the sebaceous glands. Gans [3] stated:

> It seems, therefore, worthy of recommendation that we disregard the designation of sebaceous gland adenoma, since the formations so described can in part be classed as simple hyperplasia and in part as epithelioma or epithelioma adenoides cysticum . . .

However, the diagnoses adenoma sebaceum and naevus sebaceus are well entrenched in dermatologic nomenclature and are recognized by all dermatologists as signifying definite clinical entities. Since this inclusive problem has not been discussed at length in the American dermatologic literature, it seemed advisable to analyze the cases observed at the University of Chicago Clinics in which the diagnosis was verified by

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From the Section of Dermatology, University of Chicago, The School of Medicine.

1. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 507.

2. Beck, S. C.: Epitheliome, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 3.

3. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1928, vol. 2, p. 275.

biopsy during the past thirteen years. Twenty-eight cases have been observed, classified as follows:

Adenoma sebaceum (Balzer)	1
Adenoma sebaceum (Pringle)	3
Acquired (senile) adenoma sebaceum	12
Keratotic adenoma sebaceum	1
Sebaceous gland adenoma	1
Naevus sebaceus	9
Naevus pigmentosus et sebaceus	1

ADENOMA SEBACEUM (BALZER)

The term adenoma sebaceum was first used by Balzer and Menetrier [4] in 1885. They described a patient with multiple tumors of the face, neck and scalp which appeared just before puberty and continued to develop until the time of observation. Clinically the lesions were discrete flesh-colored pinhead-sized to lentil-sized papules which presented white points resembling milia on their surfaces. Some of them had a lobular surface, but orifices were not visible. Microscopic examination revealed cellular nests with a tendency toward lobular arrangement and cystic structure. Some of these lobules were connected with normal sebaceous glands. The cells constituting the tumor masses resembled those of the basal layer of the sebaceous alveoli, which in general did not undergo the normal fatty changes. However, around many of the cysts a gradual transition from the ordinary tumor cells to cells resembling more closely those seen in the centers of normal sebaceous glands was observed. The authors concluded that the tumors were true adenomas originating in the pilosebaceous apparatus and that the cysts contained sebaceous material. In 1886 Balzer and Grandhomme [5] presented an analogous case with only minor variations.

Sutton [6] cited and agreed with Unna that the cases reported by Balzer and Menetrier and Balzer and Grandhomme were instances of multiple benign cystic epithelioma and that the cysts seen on section were not true cysts but areas containing hyaline and colloid fragments. This view has also been advocated by Beck [2] and others and is probably correct, though the contention that the cysts contain hyaline and colloid fragments has not been universally sustained. In 1922 Olson [7] adopted an entirely

4. Balzer, F., and Menetrier, P. E.: Etude sur un cas d'anénomes sébacés de la face et du cuir, Arch. de physiol. norm. et path. **6**:564, 1885; Compt. rend. Soc. de biol. **2**:313, 1885.

5. Balzer, F., and Grandhomme: Nouveau cas d'adénomes sébacés de la face, Arch. de physiol. norm. et path. **8**:93, 1886.

6. Sutton, R. L.: Differential Study of Multiple Benign Cystic Epithelioma and Adenoma Sebaceum in a Negro, J. Cutan. Dis. **29**:480 (Sept.) 1911.

7. Olson, G. M.: Adenoma Sebaceum and Tuberose Sclerosis of the Brain. Arch. Dermat. & Syph. **6**:21 (July) 1922.

different point of view when he stated that sections from a Balzer type of lesion showed alterations mostly in the hair follicles. Balzer originally described follicular changes, including thickening of the walls and destruction or atrophy of hairs, but these alterations were secondary to the formation of masses of tumor cells of sebaceous gland origin.

Ingels [8] in 1932 presented a case of a condition which he claimed fulfilled clinically and histologically the requirements for a diagnosis of epithelioma adenoides cysticum (Brooke), trichoepithelioma (Jarish), adenoma sebaceum (Pringle) and syringoma (Jacquet and Darier) and which afforded evidence to regard these conditions as manifestations of the same disease. It is probable that he was using the title adenoma sebaceum (Pringle) to indicate the lesions described by Balzer. In the same year Summerill and Hutton [9] presented a case of multiple benign cystic epithelioma and reviewed the literature to that date. They listed the cases of Balzer and Menetrier and Balzer and Grandhomme as instances of this disease without any further qualification.

Ormsby [10] credited Balzer with the first description of adenoma sebaceum and listed *adénomes sébacés* (Balzer and Menetrier) as the French synonym of adenoma sebaceum. Andrews [11] stated:

> Two types of adenoma sebaceum are recognized—the Balzer type and the Pringle type. In the former the sebaceous glands are predominantly involved, whereas in the latter the blood vessels are especially affected . . . Histologically the Balzer type shows chiefly a hyperplasia of the sebaceous glands, while the Pringle type shows a simple hypertrophy of the sebaceous gland lobule and a dilatation of the blood vessels.

MacKenna [12] listed the Balzer type as a variety of sebaceous adenoma and stated that the lesions are pale and that the changes are chiefly in the hair follicles.

Sutton and Sutton [13] under the title adenoma sebaceum stated:

> Balzer and Menétrier are usually credited with having first studied the growths microscopically, but, as Unna has pointed out, what these investigators believed to

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8. Ingels, A. E.: Epithelioma Adenoides Cysticum with Features of Syringoma, Arch. Dermat. & Syph. **32**:75 (July) 1935.

9. Summerill, F., and Hutton, J. G.: Multiple Benign Cystic Epithelioma (Epithelioma Adenoides Cysticum), Arch. Dermat. & Syph. **26**:854 (Nov.) 1932.

10. Ormsby, O. S.: A Practical Treatise on Diseases of the Skin, ed. 5, Philadelphia, Lea & Febiger, 1937.

11. Andrews, G. C.: Diseases of the Skin, ed. 2, Philadelphia, W. B. Saunders Company, 1938.

12. MacKenna, R. M. B.: Diseases of the Skin, ed. 4, Baltimore, William Wood & Company, 1937.

13. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939.

be "transformed sebaceous elements" were in reality hyaline and colloid fragments; consequently the neoplasms were not sebaceous tumors at all, but examples of epithelioma adenoides cysticum [as Pringle himself admitted].

McCarthy [14] did not refer to the Balzer type under the title of either adenoma sebeceum or epithelioma adenoides cysticum.

Case 1.—A biopsy specimen was submitted by Dr. Ruth Herrick for diagnosis. The specimen had been removed from a lobulated firm nodular lesion, 3 by 5 mm., on the tip of the nose of Miss H. T., aged 50. It had been present as long as

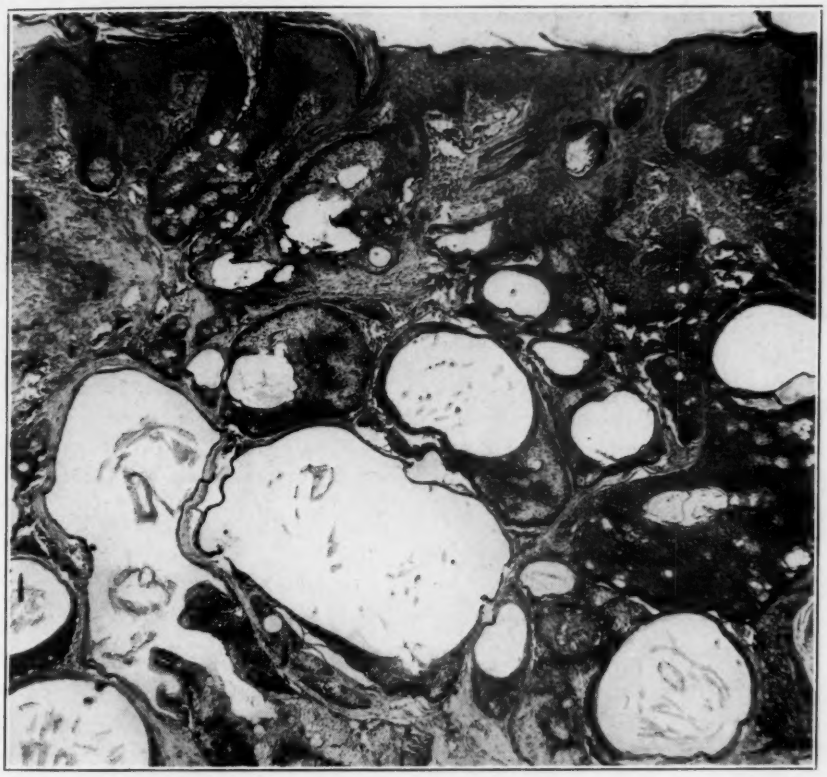

Fig. 1 (case 1).—Adenoma sebaceum (Balzer). Sebaceous gland structures are seen throughout (low power magnification; hemalum-erythrosin-saffron stain).

she could remember. The clinical diagnosis was a probable basal cell epithelioma with the possibility of a sebaceous cyst to be considered.

The following histologic observations were made: Considerable hyperkeratosis and some parakeratosis were evident, and the stratum granulosum was from 2 to 4 cells in thickness. The stratum mucosum was slightly thickened. In the corium there were many large and small islands and groups of cells (fig. 1). Cysts varying considerably in size were seen throughout the section, the smaller ones being

14. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931.

roughly in the center of the tumor masses and the larger ones appearing isolated except for some small collections of cells at their borders. The cells constituting the tumor masses were for the most part small and hyperchromatic with relatively long, oval and round nuclei and very little cytoplasm. Scattered throughout these islands were large and small collections of larger cells filled with refractile vacuoles, most of which contained nuclei. They resembled the cells seen in the center of normal sebaceous glands. The tumor masses have a tendency toward lobular arrangement, and some could be seen to be connected with hair follicles. Many dilated blood vessels were present, and scattered small collections of inflammatory cells were seen. There was a definite increase in fibroblasts, but encapsulation was not certain and was only suggested at some points.

Diagnosis was made of the Balzer type of adenoma sebaceum.

Three schools of thought have emerged as regards the nosologic position of Balzer's sebaceous adenoma, as follows: (1) as a subvariety of Pringle's sebaceous adenoma, the tumors being relatively avascular; (2) as a subvariety of Pringle's adenoma sebaceum with the lesions showing changes only in the hair follicles, or (3) as epithelioma adenoides cysticum, a variety of multiple benign cystic epithelioma. The first two seem to be untenable because they disregard the histologic observations described by Balzer and Menetrier.[4] Likewise, lesions answering the original microscopic description have not been described in association with tuberous sclerosis or epilepsy (see the section on adenoma sebaceum [Pringle]), nor have they been seen histologically in conjunction with Pringle type tumors. Furthermore, the tumors in both of Balzer's patients were present elsewhere than on the face and in 1 continued to develop long after adolescence, features not ordinarily encountered in Pringle's disease.

The conclusion of Balzer and Menetrier[4] that the lesions they described were true adenomas originating in the sebaceous glands appears to be rational. The lesions consist essentially of masses of small cells resembling basal cells, with a sufficient number of larger cells containing fat vacuoles and cysts containing sebaceous material to indicate that the tumor cells are of sebaceous gland origin and are fulfilling in part the function of such cells. There is likewise connective tissue proliferation around the tumor masses as evidence for a diagnosis of adenoma, which lessens the possibility of their resulting merely from hyperplasia of the sebaceous glands, as is perhaps the case in Pringle's adenoma sebaceum, acquired sebaceous adenoma and naevus sebaceus. Unna's contention[15] that the cysts are colloid and hyaline fragments does not appear to be correct, since their walls frequently contain sebaceous cells.

The consideration of the Balzer type of lesion as a true adenoma might seem to preclude its placement in the group known as epithelioma adenoides cysticum. However, if the latter title is used in a broad sense

15. Cited by Sutton.[6]

to indicate on the one hand prenatal disturbances of development or on the other hand benign tumors arising postnatally from the cutaneous appendages, then the condition could properly be included in that group, although some qualifying term, such as adenoma sebaceum (Balzer), is advisable.

Little information is available regarding the cause and course of this condition. It is either exceedingly rare or has not been reported because of its being considered Pringle's disease or multiple benign cystic epithelioma. Balzer's 2 patients were women; both had multiple lesions, and the mother of 1 of them had a similar eruption. One patient stated that the lesions had always been present, while the other noted them first just before puberty and the tumors were still developing in middle life. Definite diagnosis can be made only by histologic examination.

ADENOMA SEBACEUM (PRINGLE), TUBEROUS SCLEROSIS AND EPILOIA

These designations have been applied to various combinations of cutaneous tumors, visceral tumors, tuberous sclerosis, epilepsy and mental deterioration. The classic picture occurs in the syndrome known as epiloia, in which three cardinal features are present: adenoma sebaceum, epilepsy and mental deterioration, with or without visceral tumors. This subject has been recently reviewed in a superb article by Butterworth and Wilson.[16]

The cutaneous lesions in the Pringle type of adenoma sebaceum occur invariably on the face, especially in the center, or so-called rosacea area, namely, the forehead, cheeks, nose and chin. They are always bilateral and roughly symmetric and vary considerably in number. They are most numerous in the nasolabial folds and on the adjoining part of the cheeks and nose. The lesions are papules or nodules, varying in size from that of a pinhead to that of a bean. Coalescence may occasionally occur, but as a rule the tumors are discrete. Their color varies from that of the normal skin to yellowish white, yellowish or brownish red, the color representing roughly the predominant tissue constituting the tumor. Telangiectases are a common accompaniment, occurring on the surface of the lesions and between them.

A lesion of the Balzer type has been frequently described as occurring in Pringle's disease. This concept is erroneous, since Balzer's cases are evidently instances of epithelioma adenoides cysticum of sebaceous gland origin.

The histologic picture in Pringle's adenoma sebaceum varies in different cases and in separate lesions of the same patient. A typical tumor shows hyperplasia of all three elements, sebaceous glands, blood

16. Butterworth, T., and Wilson, M., Jr.: Dermatologic Aspects of Tuberous Sclerosis, Arch. Dermat. & Syph. **43**:1 (Jan.) 1941.

vessels and connective tissue. The sebaceous gland hyperplasia is evidenced by an increase in number and a more superficial location of the glands plus an increase in number of cells of the basal cell type to several layers instead of the usual single layer. Frequently the latter is the only evidence of hyperplasia. This is especially true in lesions showing a predominance of vascular and connective tissue elements. Some tumors are constituted entirely of connective tissue, but it is doubtful whether an elevated lesion is ever composed of vascular elements only. Darier seemed to believe this to be true in his case, but his clinical description of "white points" and his notation of numerous sebaceous glands histologically suggest that he may have erred in interpreting these glands as entirely normal.

In a strict sense, the pathologic change occurring in the sebaceous glands probably results from hyperplasia and does not constitute true adenomatosis. The glands retain their normal structure, and the individual cells are normal in size and not hypertrophied. Furthermore, those glands attached to hair follicles in their normal locations are usually all seen to be hyperplastic, an observation not compatible with the single point of origin expected in a true adenoma. Evidence of encapsulation is absent despite the increase in connective tissue. Nevertheless, the name adenoma sebaceum can be reasonably applied to these lesions, since Ewing [1] has urged the acceptance of a physiologic rather than a strictly morphologic concept of adenoma.

Other cutaneous lesions occur in association with adenoma sebaceum (Pringle) too frequently to be considered coincidental. Small flat fibromas, nevi, papilloepitheliomas (known as skin tags), warts, pigmented and depigmented macules, the so-called shagreen patch and peculiar lesions of the periungual and subungual regions have been described in detail by Butterworth and Wilson.[16] Pringle noted this frequent association of other "nevoid" conditions of the skin and mentioned specifically warts, pigmented nevi, molluscum fibrosum and pigmentary changes.

The diagnosis of adenoma sebaceum (Pringle) offers little difficulty. The date of onset, the location, the color of the papules and nodules, their admixture with numerous telangiectases, their permanence and the absence of suppuration combine to create a highly characteristic picture. In the presence of symptoms of tuberous sclerosis the diagnosis becomes simple indeed. Epithelioma adenoides cysticum, verruca plana juvenilis and syringocystadenoma may occasionally cause some difficulty in differentiation. In these instances microscopic examination will quickly settle the issue. It must be emphasized, however, that a diagnosis from histologic sections alone is not easy. Many sections cannot be distinguished from those of naevus sebaceus or acquired sebaceous adenoma, while others show nothing but fibrous tissue.

Adenoma sebaceum occupies a unique position in relation to the diagnosis of tuberous sclerosis and epiloia. It is beyond question the least important symptom in these combinations as regards the welfare of the patient, yet in its absence an antemortem diagnosis is virtually impossible. There is nothing especially characteristic about the mental deficiency or the epilepsy encountered in this condition, and neurologists readily admit that the cutaneous lesions are essential for a diagnosis. Even in their presence pitfalls are occasionally encountered, since the disease is uncommon and some neurologists are unacquainted with the cutaneous manifestations. One of the 2 cases reported by Stewart and Bauer [17] is an instance of this.

Wechsler [18] defined tuberous sclerosis as a chronic disease beginning in early childhood and characterized by progressive mental deterioration to idiocy, epileptic convulsions and special tumors of the skin and viscera. This syndrome with its varied manifestations is known today under the names of adenoma sebaceum (Pringle), tuberous (or tuberose) sclerosis, epiloia, Bourneville's sclerosis and Pringle's disease. As a rule the dermatologist employs the name adenoma sebaceum or Pringle's disease to designate this syndrome; whereas, the neurologist calls it tuberous sclerosis, epiloia or Bourneville's sclerosis, and the psychiatrist favors the term epiloia. Each has apparently adopted the name more nearly describing the phase of the disease in which he is especially interested. A further factor probably contributing to this multiplicity of names is the fact that the various manifestations were described independently and only later were recognized as being part of a syndrome. The syndrome was considered at length by Butterfield and Wilson.[16]

The cutaneous lesions require treatment only from cosmetic considerations. Treatment may be sought by patients after puberty and occasionally earlier by indulgent mothers. Any method of therapy employed must be destructive, but deep destruction is not necessary. Solid carbon dioxide, electrodesiccation, electrocoagulation or the actual cautery may be used. Destruction of the superficial vessels makes the condition much less conspicuous. The use of roentgen rays is not advisable, since the tumors do not respond to small doses; large doses are contraindicated, because there is danger of development of dermatitis actinica and, after all, the lesions are harmless in themselves.

CASE 2.—J. S., a 13 year old boy, was first seen in the Neurology Division of the University of Chicago Clinics on Feb 15, 1936. He had been transferred from the Children's Memorial Hospital, where a diagnosis of tuberous sclerosis, epilepsy and sebaceous adenoma had been made.

17. Stewart, H. L., and Bauer, E. L.: Tuberous Sclerosis, Arch. Path. **14**:799 (Dec.) 1932.

18. Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 4, Philadelphia, W. B. Saunders Company, 1939.

The patient had been a normal full term baby, and no difficulty had been encountered during delivery. At 1 year of age he had fallen out of a window of a one story building and had been unconscious for one-half hour. A roentgenogram of the skull had not been made. He walked at 10 months of age but did not talk until he was 3 years old. Otherwise nothing unusual was noted until he was 5 years of age, when he began to squint, became cross eyed and would grope for objects as though his vision were defective. At about the same time a permanent eruption appeared on the face which the mother attributed to the use of strong soap. He also had some "whitish" areas and elevated lesions on the trunk, which appeared somewhat later than the eruption on the face. He was fitted with glasses, which have since been changed several times.

The patient always had difficulty in school and was in a special class with no definite grading. When he was 8 years of age stammering developed, which disappeared when he was given school work more commensurate with his ability. At 11 years of age he began to have convulsions, which were irregular, occurring as often as once a day. He never lost consciousness completely and did not fall or become incontinent, but there was movement of all limbs.

The family history was incomplete; but the father was a confirmed drunkard and had left the mother frequently, and they were now separated. The mother was of limited intelligence, was on relief and was unable to grasp the significance of the patient's illness when it was explained to her. Two siblings were apparently normal.

The patient did not appear to present a serious behavior problem. He got along fairly well in school in the special class but fell asleep frequently. However, he quarreled with his sister, and neighbors complained of his behavior toward young girls.

Physical examination revealed some evident mental retardation and emotional instability. Limitation of outward movement of the right eye was present, plus a rapid rotatory nystagmus in both eyes on looking to the left and a rapid rotatory nystagmus on looking upward. Internal strabismus was present while the eyes were at rest. The chest was of the "pigeon breast" type, and a rachitic rosary was present.

Dermatologic examination showed a discrete papular eruption on the forehead, cheeks, chin, nose and nasolabial folds with some telangiectases on the surface of the lesions and between them. Several depigmented plaques were present on the trunk, plus some ordinary nonpigmented nevi on the neck and trunk. In the lumbar region there was a large plaque consisting of several slightly elevated soft flesh-colored tumors with a wrinkled surface. This was interpreted as a shagreen patch. Some discrete soft fibromas were likewise present.

A blood count and the results of urinalysis were within normal limits. The Kolmer and Kahn reactions of the blood serum were negative. A tuberculin test gave a negative result with a dilution of 1: 1,000. On examination the spinal fluid was normal. An electrocardiogram showed sinus arrhythmia with auricular premature systoles. A roentgenogram of the skull revealed diffusely scattered calcified plaques throughout the brain substance. An encephalogram showed partial visualization of the left ventricle and third and fourth ventricles, with multiple areas of calcification. There was no evidence of lateral displacement of the ventricles. A roentgenogram of the chest was essentially normal. The heart was slightly less than 10 per cent undersized, according to a film tracing. An intravenous pyelogram revealed no gross renal abnormality. Ophthalmologic examination showed alternating internal strabismus. The fundi were normal.

The boy's intelligence rating was as follows (the examination was performed elsewhere): On April 4, 1934 his intelligence quotient (Stanford-Binet) was 74, and on Feb. 3, 1935 it was 67 and he had a possible grade placement of 3A.

Microscopic examination of a section of a facial papule showed the epidermis to be essentially normal. The superficial vessels were dilated and surrounded by a minimal infiltrate consisting of a few round cells and fibroblasts. Adenomatous sebaceoeus glands were seen near the epidermis on small hair follicles. The cutis was thicker than normal, and fibrous tissue extended deeply into the adipose tissue.

A section removed from the shagreen patch on the lower part of the back showed the epidermis to be covered by a thickened but loose stratum corneum. There were several surface indentations containing a thickened horny layer. Hyperkeratosis was especially prominent about the orifices of the sweat glands. The capillaries were dilated and surrounded by a slight perivascular infiltrate consisting chiefly of fibroblasts. The cutis was thickened. The connective tissue bundles were loosely arranged and coursed in all directions, and there was more than the normal number of fibroblasts. A sweat gland and duct deep in the cutis were dilated.

Diagnosis was made of adenoma sebaceum of the face and fibroma molle of the lower part of the back. The clinical diagnosis was tuberous sclerosis (epiloia) with convulsions (major), mental retardation and adenoma sebaceum.

The patient was last seen on Feb. 17, 1938, after an absence from the clinic of about two years. His behavior had been good, but he had continued to have convulsions, about twenty attacks in the last year.

Case 3.—D. W., an 8 year old girl, was first seen in the Dermatology Division of the University of Chicago Clinics on June 30, 1937 because of an eruption on the face which had begun on the nose as flesh-colored papules and spread to the cheeks and chin, where the elements were red. The patient had consulted many physicians because of this eruption, one of whom destroyed some of the lesions with "acid," leaving scars.

There was an eruption present on the nose, cheeks, chin and lips which was most extensvie in the nasolabial folds and adjacent part of the cheeks. It consisted of reddish papules which were small and discrete. There was also a firm somewhat papillomatous tumor on the right second toe, projecting out over the toe nail.

A blood count and urinalysis gave results within normal limits. The results of a neurologic examination were entirely normal, and notations were made of the patient's alertness, good cooperation and apparently normal intelligence.

A section of tissue removed from the toe revealed thickening of the stratum corneum, which was dense and adherent and extended into many surface invaginations. The stratum granulosum was thickened, as was also the stratum mucosum. The cutis consisted of loose vascular fibrous tissue in the superficial portions and dense fibrous tissue in the deeper portion. A histologic diagnosis of verrucous papilloma was made.

A clinical diagnosis of adenoma sebaceum (Pringle) with verrucous papilloma of the right second toe was made.

Treatment was carried out by application of solid carbon dioxide, with good cosmetic results.

Case 4.—M. N., a 24 year old single woman, was first seen in the Dermatology Division of the University of Chicago Clinics because of an eruption on the sides of the nose and on the adjacent portions of the cheeks which had been present as

long as she could remember. Originally the lesions were pinkish, but they became flesh colored after treatment elsewhere with solid carbon dioxide. There was no history of convulsions or prenatal defects. The patient's father and brother had a similar eruption on the face, but her mother and sister did not. She did not know whether her grandparents had any such eruptions, but the father's siblings had none. The patient had finished high school and was a comptometer operator.

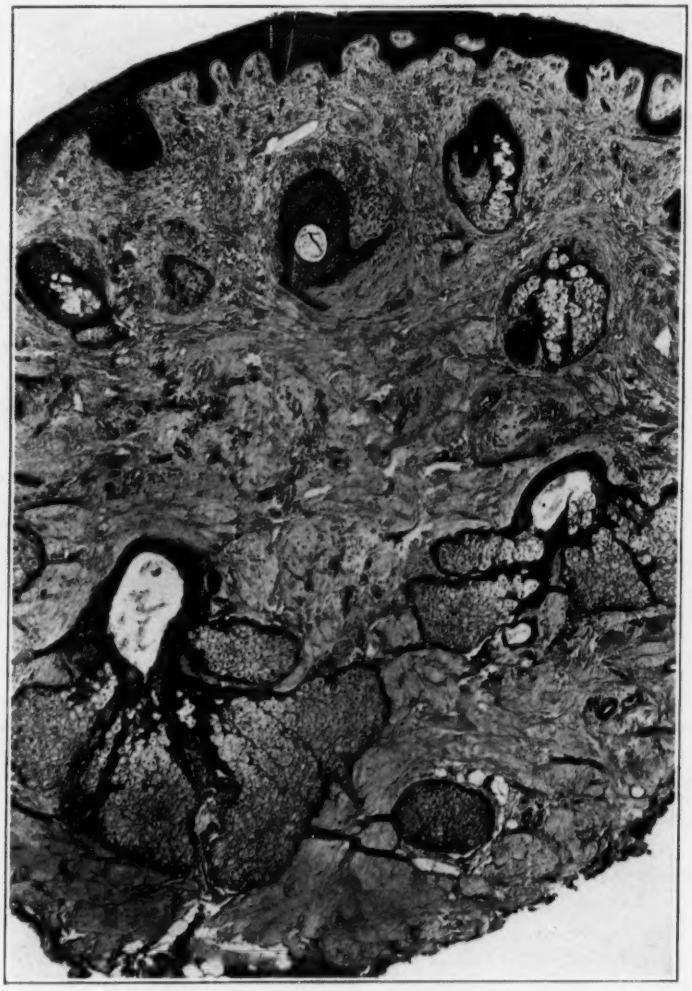

Fig. 2 (case 4).—Adenoma sebaceum (Pringle). The superficial dilated blood vessels had been destroyed by freezing with solid carbon dioxide (low power magnification; hemalum-erythrosin-saffron stain).

She had had measles, scarlet fever, whooping cough and otitis media (left ear) with some impairment of hearing in childhood. She had been told she had "leakage of the heart" but was allowed to attend gymnasium classes.

Physical examination revealed an alert, apparently intelligent patient. Examination showed no abnormalities except cutaneous lesions, a definite systolic murmur

at the apex of the heart, which was not transmitted, and some tenderness on deep palpation in the lower right quadrant of the abdomen. Many small colorless papules were present on the nose, in the nasolabial folds and on the adjacent portions of the cheeks which were discrete except for some slight coalescence. There was no telangiectasia.

The Kolmer and Kahn reactions of the blood serum were negative, and the urine was normal on examination.

Microscopic examination of a section of tissue from a facial papule showed the epidermis to be essentially normal. Only a few dilated superficial vessels were seen. Both the superficial and the deep portions of the section showed many sebaceous glands with more than the normal amount of solid cells (fig. 2). A diagnosis of adenoma sebaceum was made.

The clinical diagnosis was adenoma sebaceum (Pringle), with superficial scarring of the lesions following treatment.

The patient's brother was seen on June 29, 1939. He appeared to be of normal mentality and showed numerous small papules on the nose, cheeks, chin and forehead, which were mostly reddish to reddish brown and coalesced to a certain extent. Some telangiectasia was present. The patient stated that her eruption had a similar appearance prior to treatment.

The condition in case 2 is an example of true epiloia, and the patient will probably not survive the second decade. The three cardinal symptoms of the condition are present, but of those referable to the brain, epilepsy is decidedly in the foreground. The symptoms had not been remarkably progressive up to the time of his last visit, but it is expected that physically he will deteriorate rapidly after puberty. The onset of adenoma sebaceum was at about the average age (5 years), but convulsions appeared considerably later than usual. Most of the cutaneous changes associated with the disease were present in this patient, namely, ordinary nevi, fibromas, leukoderma and the so-called shagreen patch. The last-mentioned lesion was apparently composed of soft fibromas which had coalesced into a large patch. Retinal tumors were absent and evidence of renal tumors could not be found.

Cases 3 and 4 showed no evidence of tuberous sclerosis; hence in these instances the prognosis was good. The ocular symptoms present in case 2 are commonly seen in cases of tuberous sclerosis and are not necessarily related to retinal tumors, which were not seen in this instance. The cardiac signs elicited in cases 2 and 4 may possibly be due to rhabdomyomas, but this could be determined only at autopsy.

The familial incidence is well illustrated in case 4. Two other members of the family had probable adenoma sebaceum, and in 1 it was definitely verified. In case 2 no definite history of tuberous sclerosis or adenoma sebaceum in other members of the family was obtained, but the father was an alcoholic addict. This may represent the "psychopathic taint" so commonly found in families by Critchley and Earl [19] which

19. Critchley, M., and Earl, C. J. C.: Tuberose Sclerosis and Allied Conditions, Brain **55**:311 (Sept.) 1932.

may well result from one of the formes frustes of the disease. Furthermore, the family history was incomplete.

In 1 instance (case 2) in which the tissue was examined microscopically the hyperplasia of the sebaceous glands was not striking; only a few glands, albeit adenomatous, were present, but the vascular and fibrotic elements were predominant. However, in case 4 there was hyperplasia of the connective tissue, blood vessels and sebaceous glands, and, although the lesion had been treated, evidence of scar formation was not conspicuous and the sebaceous glands had not been destroyed by the treatment. Two important points are illustrated by these observations, namely, that these tumors probably represent adenomatous hyperplasia of the sebaceous glands, with vascular dilatation and dermal fibrosis rather than formation of true adenoma of the sebaceous elements, and that diagnosis from a histologic section alone may be difficult.

ACQUIRED (SENILE) SEBACEOUS ADENOMA

This designation is employed for a rather common cutaneous condition appearing on the face of seborrheic persons after puberty. In most instances diagnosis can be made clinically; consequently most of our biopsy specimens were from atypical papules. When fully developed the typical lesions are yellowish, irregularly round, flat-topped, frequently umbilicated papules. They are commonly located on the forehead and nose but may be found elsewhere on the face. Their number varies within wide limits. Nomland [20] observed that they varied from less than a dozen to more than fifty. Nine of our 12 patients presented but a single lesion each; 1 patient had two lesions, and 2 patients had three lesions each. It is possible that isolated lesions are common but that little attention is paid to them, since they resemble nonpigmented nevi and in many instances are noted during examination for other conditions. When multiple tumors are present, their location may be bilateral but they are always asymmetric.

On microscopic examination the principal alteration is hyperplasia of the sebaceous glands. Their arrangement is relatively normal, but there is an increase in the number of acini, which as a rule are superficially located. Collections of solid cells are commonly seen, especially as a continuation of the sebaceous gland duct. Cystlike degeneration of moderate degree is present in a majority of specimens. Hyperplasia of the connective tissue is more common than in naevus sebaceus but is of little value as a diagnostic criterion. True encapsulation is not observed. The epithelium is usually atrophic, probably because of the pressure of the glands beneath it. In some instances dilated follicular orifices are

20. Nomland, R.: Senile Sebaceous Adenoma, Arch. Dermat. & Syph. **22**:1004 (Dec.) 1930.

present, but this feature is not as prominent as it is in naevus sebaceus. In general it may be stated that there is little difference histologically between the latter condition and acquired adenoma sebaceum.

There is some difference of opinion as regards the nosologic position of this disorder, but it is actually not as great as it first appears. Most American dermatologic textbooks have adopted the name senile sebaceous adenoma for the lesions, but there is little support for such a diagnosis in the literature. Unna [21] described the lesions in 1894 and considered them to result from hypertrophy of the sebaceous glands, an idea shared by Crocker.[22] Darier [23] and Brocq [24] discussed them in their textbooks under the name *adénomes sébaces non symétriques.* Ormsby [10] stated that he had long viewed the condition as compound milium but had adopted the name senile sebaceous adenoma, suggested by Nomland in 1930. Nomland [20] concluded that the growths were true adenomas but admitted that they consist of normal-appearing acini. In 1 case he observed at least eleven follicles contributing to the growth, which is in itself a strong argument against a diagnosis of adenoma. Both Gans [3] and McCarthy [14] placed this condition with nevi of the sebaceous gland but raised the question as to whether it might not represent a purely functional hypertrophy or hyperplasia.

Gilman [25] in an interesting study, including construction of a wax model, objected to the designation of the lesions as either nevi or adenomas. He pointed out that the glands constituting the tumors are normal except for their complexity and size, that their arrangement is orderly and that they are all connected to follicles. He suggested the name adenomatoid sebaceous hyperplasia and believed the condition was produced by Demodex folliculorum. Weidman, in discussing the presentation, agreed with Gilman that there is nothing disorderly about the arrangement of the glands and that the alteration merely constitutes hyperplasia. Hirschfeld [26] concluded from a study of 4 cases that the condition is due purely to hyperplasia.

A definite cause for this disorder has not been established. Hirschfeld [26] observed the skin of his patients to be otherwise normal for their age, and he emphasized that neither seborrhea nor rosacea was present.

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21. Unna, P. G.: Die Histopathologie der Hautkrankheiten, Berlin, A. Hirschwald, 1894, p. 816.

22. Crocker, H. R.: Diseases of the Skin, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1905, p. 1131.

23. Darier, J.: Précis de dermatologie, ed. 4, Paris, Masson & Cie, 1928, p. 969.

24. Brocq, L.: Précis-atlas de pratique dermatologique, Paris, Gaston Doin, 1921, p. 1172.

25. Gilman, R. L.: Adenomatoid Sebaceous Tumors with Particular Reference to Adenomatoid Hyperplasia, Arch. Dermat. & Syph. **35**:633 (April) 1937.

26. Hirschfeld, B.: Ueber senile (und präsenile) rein hyperplastische Talgdrüsentumoren, speziell des Gesichts, Arch. f. Dermat. u. Syph. **72**:25, 1904.

On the other hand, Nomland observed either one or both of these abnormalities present in all 5 of his cases. While definite notes were not made in all instances, it is our distinct impression that all of our patients with multiple lesions of acquired adenoma sebaceum had pronounced seborrhea.

Acquired sebaceous adenoma occurs in middle-aged and elderly persons, usually after the fourth decade. Instances have been recorded of its occurrence earlier in life. Gilman's patient stated that the lesions had been present since the age of 18,[25] and Reitman [27] mentioned that he had seen the condition in a patient aged 29. In our series the ages

Fig. 3.—Adenoma sebaceum of the acquired or senile variety (low power magnification; hemalum-erythrosin-saffron stain).

ranged from 33 to 75, with the majority of patients over 50 and the average 54. Women were more frequently affected than men, in the ratio of 9 to 3, but the series was too small for the figures to be significant. Gilman [25] considered Demodex folliculorum to be causative, but the causal relation of this ubiquitous organism is just as debatable here as in other dermatoses which have been attributed to it. The associated dermatoses present in our series are characteristic of involutional changes not uncommonly seen in patients beyond middle age.

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27. Reitman, K.: Zur Kenntnis der Talgdrüsen und der von ihnen ausgehenden Wucherungs- und Neubildungsprozesse, Arch. f. Dermat. u. Syph. **99**:125, 1910.

We have taken biopsy specimens from 12 patients, whose ages varied from 33 to 75. The lesions were solitary in 9 and multiple in 3. One patient also presented keratosis seborrhoeica (epithelioma: authors); 1 presented keratosis seborrhoeica and senile keratosis; 1, epithelioma (carcinoma: authors); 1, keratosis seborrhoeica and epithelioma, and 1 sebaceous cyst of the scalp. The locations of the lesions were as follows: on the nose in 7 instances, on the forehead in 5 instances and on the cheeks in 2 instances.

The sections studied in the 12 cases of this series permit of no other interpretation than that of simple adenomatosis. Aside from the more superficial location of the lobules and the presence of small collections of solid cells, the glands were normal in structure and arrangement (fig. 3). There was nothing disorderly about their appearance, and they apparently continued to function. The glands usually arise from several follicles and thus fail to exhibit the single point of origin expected in a true adenoma. Cystic degeneration is a minor feature and is too infrequent to indicate disturbed function or lack of outlet. Connective tissue proliferation occurs in many of these growths, but this tissue is not especially prominent and never forms a true capsule. Thus the only justifiable diagnosis is that of hyperplasia, and an acceptable designation for this condition would be acquired sebaceous adenomatosis. The descriptive term senile is not a proper one, since senility is not a requisite for their development. An alternate title is that of Gilman,[25] namely, adenomatoid sebaceous hyperplasia.

KERATOTIC ADENOMA SEBACEUM

In 1 instance in which a diagnosis of possible keratosis senilis had been made, microscopic examination revealed acquired sebaceous adenoma with epidermal hyperkeratoses. The latter change was localized about the orifice of groups of adenomatous sebaceous glands (fig. 4), three of which had been removed for biopsy. The epidermis was dense and hyperkeratotic, with no parakeratosis. The epithelium showed none of the changes characteristic for keratosis senilis, and there was no cellular infiltrate in the cutis as is usually seen in this condition. The clinical appearance of a keratotic lesion a few millimeters in diameter, along with the microscopic observations, would seem to justify a diagnosis of keratotic adenoma sebaceum. The patient had serborrhea, was 47 years of age and had noted the lesions for several years.

ADENOMA OF SEBACEOUS GLANDS

In spite of Gans's statement [3] that true adenoma of sebaceous glands does not exist, it would seem unusual if a structure as primitive as the sebaceous glands did not occasionally undergo true benign neoplasia.

Mallory [28] stated that benign tumors with the characteristics of sebaceous glands are rare. He presents a description of an adenocystoma "larger than one's fist" removed from a man's neck. The numerous cysts were filled with a clear oil, which on cooling and solidifying was of the color

Fig. 4.—Adenoma sebaceum (keratotic) (low power magnification; hemalum-erythrosin-saffron stain).

and consistency of butter. The following case seems to justify a diagnosis of sebaceous gland adenoma:

Case 5.—A specimen submitted for diagnosis by Dr. H. Tannenholz had been removed from a small tumor which had been noted by a man aged 56 for two or

28. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914.

three months on the outer aspect of his left thigh. The lesion was roughly conical and measured about 0.5 cm. in diameter at its base. There was a button-like firmness on palpation, and a few telangiectatic vessels coursed over its surface. Fibroma, subepidermal fibrosis and fibrosarcoma were considered in the clinical diagnosis.

Microscopic examination showed the epidermis to be essentially normal except for slight hyperkeratosis and thinning of the rete mucosum in one area. In the cutis a short distance below the basal layer there was a well encapsulated tumor mass (fig. 5). It was composed of groups of hyperchromatic cells with relatively large vesicular nuclei and little cytoplasm intermixed with large vacuolated cells resembling sebaceous gland cells (fig. 6). Some small areas had undergone simple necrosis. Many small cystlike spaces were scattered throughout the lesion, and in the center was a large brownish-staining homogeneous mass resembling the contents of a sebaceous cyst. The large vacuolated cells predominated, and there was no semblance of order in their arrangement or in their relation to the other cells present. Occasional mitotic figures were seen. Widely dilated blood vessels were numerous within the tumor. There was no connection with the surface, and a definite connective tissue capsule could be distinguished. A diagnosis was made of true adenoma of sebaceous gland origin. The possibility that the lesion might represent early epithelioma of the sebaceous glands was also considered.

NAEVUS SEBACEUS

A prenatal variety of adenoma sebaceum was first described by Jadassohn [29] in 1895 and is known as naevus sebaceus. He differentiated this condition from the various types of adenoma sebaceum and considered it a nevoid growth composed partly or entirely of sebaceous glands of normal structure. Since that time only limited attention has been paid to this condition in the literature, and Robinson [30] could find reports of only 35 cases up to 1932. His paper, in which he reported 4 cases of his own, adequately covered the literature to that date, including 1 case in the English literature, that of Olsen, which is, however, of Pringle's adenoma sebaceum and not of naevus sebaceus. Additional reports in English have been presented by Gottheil [31] in 1901 and Maloney [32] in 1934.

It is generally stated that the sebaceous glands comprising the naevus sebaceus tumors are normal in structure and arrangement. Jadassohn [29] originally expressed such a view, which has been supported by Bandler,[33]

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29. Jadassohn, J.: Bemerkungen zur Histologie der systematisierten Naevi and über Talgdrüsennaevi, Arch. f. Dermat. u. Syph. **33**:355, 1895. Werner, A.: Zur Kenntnis der "systematisierten Naevi," ibid. **33**:341, 1895.

30. Robinson, S. S.: Nevus Sebaceus (Jadassohn): Report of Four Cases, Arch. Dermat. & Syph. **26**:663 (Oct.) 1932.

31. Gottheil, W. S.: Adenoma Sebaceum of the Non-Symmetrical Type, J. A. M. A. **37**:176 (July 20) 1901.

32. Maloney, E. R.: Nevus Sebaceus Linearis: Case Presentation, Arch. Dermat. & Syph. **30**:167 (July) 1934.

33. Bandler, V.: Zur Histologie des Naevus sebaceus, Arch. f. Dermat. u. Syph. **49**:95, 1899.

Gottheil,[31] McCarthy [14] and others. Kyrle,[34] however, pointed out that although normal glands may be present, their basal layers are usually atrophic or absent. Robinson [30] reported similar observations in 3 of 4 cases. McCarthy [14] claimed that in some tumors the sebaceous elements may almost or entirely disappear and be replaced by dense fibrous tissue. This is contrary to the generally expressed opinion that the connective tissue does not take part in the formation of these lesions. Robinson [30] found the collagen and elastin entirely normal in all 4 of his cases.

A subtype of naevus sebaceus was described by Wolters [35] in 1910 under the name naevus epitheliomatosus sebaceus capitis. It occurs on the scalp, most often in the parietal region, and is a unilateral circumscribed yellow hairless plaque with a smooth uneven surface. According to McCarthy, the histologic picture of these lesions is practically the same as that of naevus sebaceus except that occasionally the glands may be entirely absent and small collections of epithelial cells originating from dilated hair follicles and enclosing a downy hair are seen.

Ormsby [10] failed to mention naevus sebaceus in his textbook, but the lesion he described under the name milium congenital (en plaques) was apparently the same condition. He credited its description to Crocker, Hebra and Wilson. The condition called adenoma sebaceum circumscriptum by Audry [36] likewise corresponds closely to naevus sebaceus.

Naevus sebaceus is present at birth or appears early in life. Occasionally it is described as occurring later, but such conditions are possibly examples of acquired (senile) sebaceous adenoma, since the two may be practically indistinguishable histologically. Our accumulation of 10 cases in seven years suggests that it is not as rare as is frequently believed, especially since we included only those cases in which the diagnosis was verified by histologic study.

Clinical Features.—The clinical diagnosis in typical instances is not especially difficult. The lesions occur in plaques of various sizes, rarely over 5 cm. in length, and are circumscribed yellowish flat firm plaques with a granular or furrowed surface. The last-mentioned change is occasioned by the fact that the plaques are composed of small round closely set papules. Pitting may be seen and is due to enlarged follicular orifices. The plaques are commonly unilateral and rarely multiple. On the scalp they are devoid of hair and may be verrucous. Occasionally the individual papules comprising the tumor are arranged in linear

34. Kyrle, J.: Histobiologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1925.

35. Wolters, G.: Ueber einen Fall von Naevus epitheliomatosus sebaceus capitis, Arch. f. Dermat. u. Syph. **101**:197, 1910.

36. Audry, C.: De l'adénome sébacé circonscrit, Ann. de dermat. et syph. **4**:563, 1903.

Fig. 5 (case 5).—Adenoma of a sebaceous gland. Encapsulated tumor (low power magnification; hemalum-erythrosin-saffron stain).

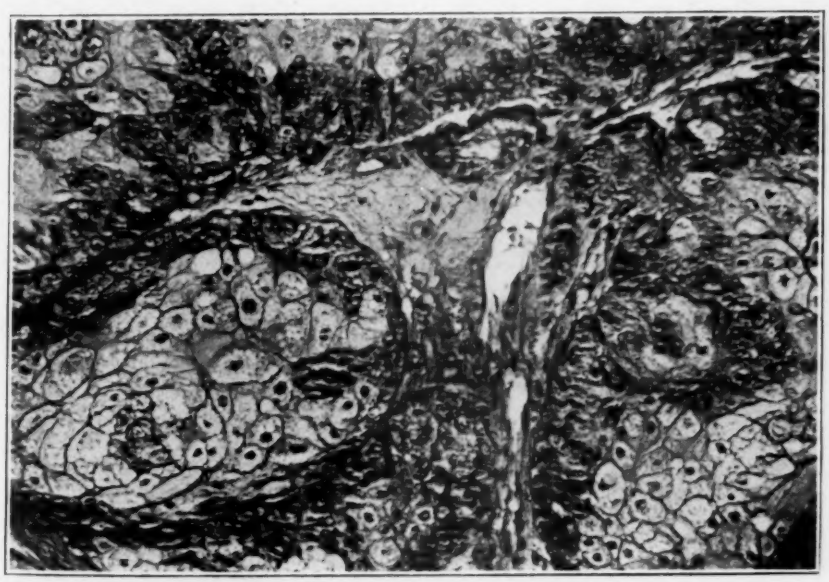

Fig. 6 (case 5).—Adenoma of a sebaceous gland (high power magnification; hemalum-erythrosin-saffron stain).

fashion, in a somewhat zosteriform pattern, and are spoken of as being systematized. The lesions in 1 of our patients exhibited such an arrangement.

As a rule patients display but a single plaque consisting of from one to many individual papules. Nine of our 10 patients had but a single tumor, the tenth showing several lesions, some of which may have been ordinary nevi. Confusion in diagnosis is encountered most frequently when the lesion consists of a single papule. Thus in 6 of 8 cases in which an impression was recorded naevus sebaceus was the only clinical diagnosis considered; in the other 2 the lesions were thought to be ordinary nevi. Gottheil [31] diagnosed the dermatosis in his case clinically as xanthoma and stated that Darier admitted that the lesions cannot be diagnosed without microscopic examination. Robinson [30] listed several conditions that may be or may have been confused with naevus sebaceus. In our experience such difficulty is the exception rather than the rule, except in the case of small isolated lesions.

Microscopic Features.—Pathologically naevus sebaceus represents hyperplasia of the sebaceous glands. The glands are increased in size and number but retain their normal arrangement, are frequently attached to follicles and probably continue to function. Other structures do not enter into the formation, and the lesions are never encapsulated. Robinson [30] observed that most of the glands in his cases had no connection with follicles and lay free in the cutis. Studies of single sections frequently give this impression, but when serial sections are examined more and more glands can be seen to empty into follicles. It is probable that the majority of them do so. This is suggested by Gilman's wax model of adenomatous sebaceous hyperplasia,[25] which showed all glands to have surface outlets. While this model was not of a sebaceous nevus, the lesion is pathologically similar. Furthermore, cystlike degeneration of the sebaceous cells, while frequent, is never extensive enough to suggest that most of the glands have no outlet. Usually only a few small cystlike areas are seen, and occasionally they are entirely absent.

There are two objections to Jadassohn's observation [29] that the sebaceous glands are normal in structure. In the first place, as pointed out by Kyrle,[34] the basal layer is frequently atrophic or absent. To this must be added what appears to be more important, namely, that in parts of all such tumors abnormally large amounts of solid epithelial cells of the basal cell type may be found. This usually occurs toward the distal end of the glands but may be seen on the sides and in the centers. It represents the best evidence of hyperplasia, along with the increase in number and size of the acini and their more superficial location.

The follicular orifices in these tumors are almost invariably widely dilated and filled with sebum and horny material, a fact recently stressed

by McKee.[37] Not all of the follicles in a single lesion are so involved. The sweat glands may rarely show hyperplasia. Wolters [35] described abnormalities of sweat glands, and in 1 of our cases there were both hyperplasia and degenerative changes. The elastin and collagen do not take part in the process, and the inflammatory cells frequently seen are probably due to irritation.

The greatest difficulty is encountered in attempting to distinguish naevus sebaceus histologically from acquired sebaceous adenoma. Both tumors are composed of hyperplastic sebaceous glands of a similar character; neither is encapsulated, and cystlike degeneration occurs in both lesions to a similar degree. The only possible clue is the almost invariable occurrence of widely dilated follicle mouths in naevus sebaceous, which are seen only occasionally in acquired sebaceous adenoma. This cannot be relied on too strongly, and the diagnosis must rest on history and clinical appearance. Adenoma sebaceum (Pringle) may also cause difficulty, depending on the predominance of sebaceous glands in the particular lesion examined. Balzer's adenoma sebaceum can be readily differentiated.

Naevus sebaceus thus appears to be produced by prenatal hyperplasia of sebaceous glands, is entirely benign and is of cosmetic interest only. It may occasionally be associated with naevus pigmentosus. Gilman [25] correctly objected to the term nevus being used to designate this condition. Treatment is readily carried out by means of cautery, electrodesiccation, coagulation or excision. Slight scarring is inevitable, but recurrence is rare. McKee,[37] however, insisted that the tumors recur unless excised.

NAEVUS PIGMENTOSUS ET SEBACEUS

Adenomatous sebaceous glands are at times observed in association with other abnormalities which have often been designated as nevi. The verrucous type of naevus unilateralis when present on the scalp often includes such glands. A combination with pigmented nevi may also be seen. The following case is illustrative:

Case 6.—Mrs. M. K., aged 39, presented four small tumors on the nose and forehead which had been present all her life. The clinical impression was that of naevus pigmentosus. Microscopic examination showed that the epithelium was definitely thinned and a single widely dilated, plugged follicle was present. In a large portion of the corium there were many groups of typical nevus cells; close to this area and actually overlapping there were many hyperplastic sebaceous glands with considerable increase in solid cell elements. Sebaceous glands were seen to be connected to the only follicle present. Diagnosis was made of naevus pigmentosus et sebaceus.

37. McKee, G. M., in discussion on Maloney.[32]

SUMMARY

Analysis is made of 28 cases of various types of adenomatosis of the sebaceous glands.

The condition may be divided into seven groups: adenoma sebaceum (Balzer), adenoma sebaceum (Pringle), acquired (senile) adenoma sebaceum, keratotic adenoma sebaceum, sebaceous gland adenoma, naevus sebaceus and naevus pigmentosus et sebaceus.

Adenoma sebaceum (Balzer) belongs in the group of multiple benign cystic epithelioma.

Keratotic adenoma sebaceum and sebaceous gland adenoma have evidently not been reported previously.

The literature is reviewed; much confusion exists relative to the various members of the group, especially between the Balzer and the Pringle varieties of adenoma sebaceum.

Careful clinical and especially microscopic study are necessary for accurate evaluation.

While the lesions in a majority of the members of the group do not represent true adenomas, the designations are convenient and satisfactory, in view of the uncertainty which exists relative to the use of the term adenoma.

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SECONDARY INFECTION OF CUTANEOUS LESIONS WITH CORYNEBACTERIUM DIPHTHERIAE

ELMORE B. TAUBER, M.D.†
AND
LEON GOLDMAN, M.D.
CINCINNATI

In our clinical study of diphtheria of the skin we have limited ourselves to an analysis of the particular phase known as "secondary diphtheria" or "wound diphtheria." There is considerable controversy about this type because it is difficult to determine the exact role of the diphtheria organism. This confusing condition must be differentiated from the many forms of acute and chronic primary diphtheria of the skin. In the primary form, the bacterial flora of the lesion is predominantly, or entirely, diphtheritic even from the onset; cure is obtained by administration of antitoxin, and true postdiphtheritic visceral complications may occur. In the secondary form, the cutaneous lesion is not initiated by the diphtheria organisms, which are found usually by chance or in epidemic surveys; the value of antitoxin is doubtful, and complications are rare. It is possible that the secondary form is commoner than one supposes, but routine bacteriologic surveys of "ordinary" lesions of the skin are not often made.

In the first place, one must be sure that Corynebacterium diphtheriae itself is present. The differentiation between the diphtheria and the diphtheroid organisms as to morphologic characteristics, fermentative reactions and virulence tests should be made by the trained bacteriologist, not by an inexperienced technician or by an uninformed clinician. The intracutaneous virulence test usually employed is simply the injection of 0.2 cc. of a seventy-two hour culture intracutaneously in the ventral skin of guinea pigs. Redness, swelling and necrosis in forty-eight hours mean that the culture is virulent.[1] The virulence test is probably the most important part of the analysis. Figures for carriers of virulent bacilli in the nose and throat vary, according to various factors, from 0.2 to 1 per cent. For carriers of avirulent bacilli the percentage is approximately twice as large. Stebbins,[2] in a recent survey of diph-

† Dr. Tauber died June 24, 1941.

From the Department of Dermatology and Syphilology of the University of Cincinnati College of Medicine.

1. Grossmann, W.: A Schick Test and Diphtheria Carrier Survey of White School Children in Virginia, Am. J. Pub. Health (supp.) **30**:9 (March) 1940.

2. Stebbins, E. L.: Diphtheria Immunity and Carrier Surveys in New York State, Am. J. Pub. Health (supp.) **30**:39 (March) 1940.

theria carriers, found figures as low as 0.03 and 0.07 per cent for virulent forms.

On healthy skin it is rare to find virulent bacteria even when faucial diphtheria is present. On the other hand, avirulent diphtheria-like bacteria are not uncommonly found on the skin which is free of lesions, especially in the genital regions. When various types of cutaneous lesions are present, the problem becomes more complex. Santori,[3] who has done considerable work with diphtheria of the skin, examined the cutaneous lesions in cases of various types of dermatitis and found a carrier rate of the relatively high figure of 3.3 per cent. In the majority of cases the same organisms were also found in the nose and throat; in some cases the bacteria were found only on the skin. He observed the highest frequency of positive cultures in children between the ages of 4 and 10 years. None of the strains isolated from middle-aged or elderly patients was virulent. Santori also studied the diphtheroid bacteria on the skin. He too believed these were "met with a notable frequency" on healthy skin. From patients with ulcerations, 57 per cent more positive cultures of diphtheroid than of diphtheria bacteria were isolated.

There have been reports in the literature on the secondary type of diphtheritic infection of the skin, especially in epidemic forms. Fitzgerald and Robertson [4] described a series of 32 patients whose source of infection was probably a diphtheritic lesion on the finger of a nurse. Weinert [5] and Nieter [6] each reported a series of cases. Weinert claimed that the nursing personnel contracted actual faucial diphtheria from "wound diphtheria." Of 497 patients Nieter observed that 286 (58.6 per cent) had positive cultures. Virulence tests were made in 8 cases. Most of the cultures of the throat in his cases of "wound diphtheria" were reported to be negative.

We have had the unusual opportunity to study briefly the effect of a diphtheritic infection which spread throughout a dermatologic ward. After the appearance of faucial diphtheria, which occurred in a patient in the otolaryngologic ward, it was decided to examine all the dermatologic patients. The otolaryngologic ward was adjacent to the derma-

3. Santori, G.: Sulla presenza di bacilli difterici e pseudo difterici sulla cute humana sana od ammalata, Gior. ital. di dermat. e sif. **80**:307 (April 2) 1939; abstracted, Ann. de dermat. et syph. **10**:821 (June) 1939.

4. Fitzgerald, J. A., and Robertson, D. E.: Report of an Outbreak of Diphtheritic Wound Infection Among Returned Soldiers, J. A. M. A. **69**:791 (Sept. 8) 1917.

5. Weinert, A.: Wund- und Narbendiphtherie, München. med. Wchnschr. **66**:235 (Feb. 28) 1919.

6. Nieter, A.: Zur Wundiphtherie in Magdeburg, München. med. Wchnschr. **66**:239 (Feb. 28) 1919.

tologic ward. The nursing and orderly personnel served both wards; moreover, ambulatory patients from both wards frequently congregated. No cases of diphtheria were reported in other wards of the hospital at that time. Shortly before this study was made culture of material from the nose and throat of a patient in the far removed female surgical ward showed diphtheria organisms. In a few days, however, the cultures were repeatedly negative. A gluteal abscess, from which the patient suffered, at no time revealed diphtheria organisms. No additional patients in the surgical ward were examined. Not one of the dermatologic patients had signs of faucial diphtheria or any suggestion of cutaneous diphtheria. The swabs were streaked on Loeffler's medium and incubated over night. They were examined at the central laboratory of the Cincinnati General Hospital and the laboratory of the contagious disease unit of the hospital.

Eighteen patients and the entire medical nursing and orderly personnel were examined. Cultures of material from the nose and throat and of the skin were obtained in each instance. Of the 18 patients only 2 had negative cultures on first examination. Of the 16 patients with suggestive and positive cultures only 1 had a negative culture of material from the nose and throat with a positive culture of the skin. Three positive reactions to virulence tests were obtained with organisms from cutaneous lesions. None of the patients who had such a reaction had any postdiphtheritic sequelae. The value of the antitoxin (5,000 units given in 7 cases, 10,000 units in 2 cases and none in the remainder) could not be determined. In many of the cases, cultures "spontaneously" became negative on repeated examinations. Many of the patients were discharged from the hospital and were reported to the Board of Health. Nine patients who were unable to leave the hospital were transferred to the contagious disease unit. In addition, the entire medical, nursing and orderly personnel of the dermatologic ward was examined as regards cultures of material from the nose and throat and of the skin, and no positive or suspicious cultures were reported. Unfortunately, no extensive performing of Schick tests was carried out. No single case of faucial diphtheria was encountered. As far as could be determined, none of the patients discharged from the hospital caused any spread of diphtheria. In this small group of cases, then, the presence of C. diphtheriae in the cutaneous lesion had no effect on the cutaneous lesion itself and caused no visceral lesions.

Later, a control bacteriologic survey was made of the patients in the dermatologic wards. In the first series 8 patients from the children's ward, suffering from burns, were examined, and cultures were obtained from the nose, the throat and the burns. In this children's ward suggestive cultures were found in only 1 child, and that child was discharged and not followed. Several months later the entire adult dermatologic ward was examined. Cultures from only 2 of 20 patients showed diph-

theria organisms; these positive cultures did not persist on repeat examinations and no virulence tests were made. The presence of these organisms had no effect on the clinical course of either patient.

At the same time the patients in the otolaryngologic ward, adjacent to the dermatologic service, were examined. Of the 13 patients studied, 2 were found to be carriers of diphtheria organisms. These 2 showed positive cultures also from swabs rubbed over the clear skin of the cheek. Virulence tests showed these organisms to be nonvirulent. A distant surgical ward was then studied, and 8 patients were selected at random. Not one of these had any diphtheria organisms in cultures.

To establish another set of controls, 11 patients who had essentially chronic nonulcerative lesions of the skin were taken at random from the dispensary. This brief study was made during February and March 1941. Only 1 patient had a positive culture from the skin, and this, curiously, was from an area of vitiligo. The virulence tests of this patient and of 1 with a doubtful culture from the skin gave negative results.

SUMMARY

In a dermatologic ward of 18 patients a secondary infection of C. diphtheriae spread from a sporadic case of faucial diphtheria in an adjacent otolaryngologic ward. The two wards were served by the same nursing and orderly personnel. Sixteen of the dermatologic patients had morphologically true diphtheria organisms in the various lesions of the skin. The results of virulence tests, which were performed in a few instances, were positive. Small doses of antitoxin were given, but the effect of this could not be evaluated critically. There were no postdiphtheritic sequelae. The condition in these cases was considered to represent a type of secondary asymptomatic diphtheritic wound infection. No diphtheria organisms were found in the medical, nursing or orderly personnel. Control surveys of cultures of material from the nose and throat and of the skin in the dermatologic wards and dispensary and also in other wards at a later time revealed only an occasional positive culture of diphtheria organisms from the skin.

Most of the cultures were examined by Dr. Ethel Hopphan, of the central laboratory of the Cincinnati General Hospital. Bacteriologists at the contagious unit examined the remainder of the cultures. Dr. Frank E. Stevenson, of the department of pediatrics, made a critical survey of the data presented.

441 Vine Street.

Clinical Notes

NEW TECHNIC FOR MAKING PATCH TESTS: USE OF PYREX CUPS

JAMES H. STERNER, M.D., ROCHESTER, N. Y.

In making patch tests with solutions or powders, the use of small pyrex cups has proved to be satisfactory.

The cups, made from 1 mm. pyrex, measure 15 mm. in diameter by 5 mm. deep. The ground rim should be fire glazed so as not to cut the skin. The cups are

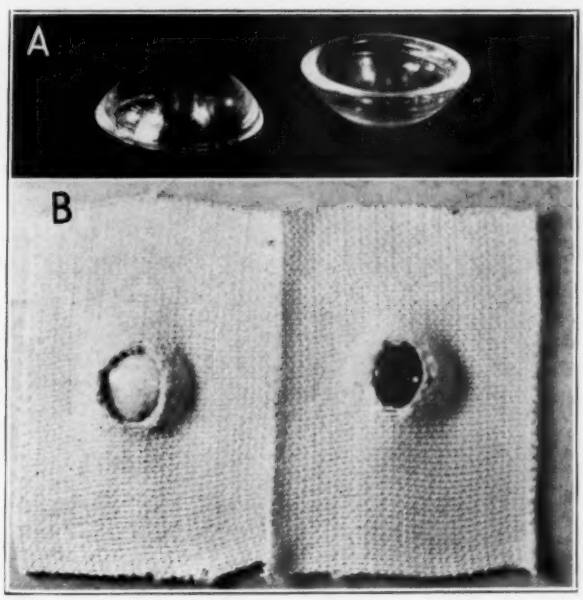

Fig. 1.—*A*, pyrex cups for patch tests. *B*, cups held in contact with the skin by elastic adhesive tape.

held in firm contact with the skin by means of elastic adhesive tape, which may be perforated to show the contents of the cup. A moderately firm 10 mm. ball of cotton is moistened with the test solution, or impregnated by being rolled in the powdered test material, and put in the pyrex cup.

The advantages of this method over the customary formation of a flat transparent "window" are as follows: 1. The test is confined to a small sharply defined area. 2. Any type of solvent indicated may be used. 3. The solvent is better retained in contact with the skin for the duration of the test. 4. The patches are easily prepared in advance and quickly applied.

From the Laboratory of Industrial Medicine, Eastman Kodak Company.

The cups can be used again. They may be soaked in gasoline to remove the adhesive tape, and then fuming nitric acid, a water rinse, strong sodium hydroxide and copious water rinsing will remove all traces of the test material.

The cups used were made by Mr. F. J. Shedd, Precision Optical Company, 38 Geneva Street, Rochester, N. Y. They are not patented.

Eastman Kodak Company.

A RATIONAL APPLICATION FOR PUSTULAR ACNE: SULFUR LOTION WITH SULFATHIAZOLE

THOMAS S. SAUNDERS, M.D., PORTLAND, ORE.

The use of sulfur (in its various feebly bacteriostatic forms) in the local treatment of pustular acne has never seemed rational. I have not been surprised at the poor results obtained.

Recently I have been adding 5 per cent sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) to the ordinary sulfur shake lotion and have found that the number of pustules is usually conspicuously reduced after the patient has used the preparation for three weeks. I feel that the sulfathiazole portion of the lotion is responsible for the reduction of pustules, while the sulfur portion has the usual keratolytic effects.

Medical Arts Building.

Correspondence

NUMMULAR ECZEMA

To the Editor:—It seems certain that the interesting paper by Dr. Paul Gross on nummular eczema (ARCH. DERMAT. & SYPH. **44**:1060 [Dec.] 1941) will arouse a great deal of interest in dermatologic circles as a notable contribution regarding this stubborn condition.

Thanks to an abstract in the 1939 Year Book of Dermatology and Syphilology (page 452), I was led to treat a series of patients with nummular eczema during the past two years with preparations of vitamin A—by mouth, 24,000 international units night and morning, and by parenteral injection, 100,000 international units twice weekly. I must confess that the results, though often encouraging, were also often disappointing, and recurrence sometimes appeared while a patient was still taking the full dose of the vitamin, though it was noticeable that persons with particularly dry skins and those whose rash appeared to be worst in winter had the best results.

Two small points which I have noted in connection with this treatment may be of interest; several of the patients treated remarked spontaneously that they were at last able to luxuriate in really hot baths without their skin's being affected in the least, while others stated that their "nerves" seemed to be much steadier and that they now slept much more soundly.

G. A. GRANT PETERKIN, Edinburgh, Scotland.

Obituaries

DOUGLASS W. MONTGOMERY, M.D.
1859–1941

Douglass William Montgomery died at the age of 82 in Guayaquil, Ecuador, on Dec. 21, 1941, from an attack of coronary thrombosis. He was accompanied by his devoted wife and constant companion, who was always with him on his travels.

He was born in Islington, Ontario, Canada, of Scotch and Welsh parents, on Aug. 3, 1859. His father, William J. Montgomery, was a farmer and later a capitalist. Three of his uncles and one brother were physicians. His first wife, who died in 1908, was Ellen Sargent, daughter of Aaron Sargent, United States Senator from California and Minister Plenipotentiary to Germany. In 1910 he married Charlotte B. Spring, daughter of Francis S. Spring, of San Francisco. He leaves a son and daughter by his first wife, the son residing in Toronto, Canada, and the daughter (Mrs. E. M. Deaton) in Berkeley, Calif.

Dr. Montgomery graduated from Upper Canada College and received his medical education at Toronto School of Medicine and at Columbia University College of Physicians and Surgeons, New York, graduating from the latter institution in 1882. He then spent three active years in postgraduate study in Italy, Heidelberg, Wurzburg, Vienna, Switzerland, London and finally Edinburgh.

He was professor of pathology at the University of California from 1888 to 1892 and professor of cutaneous diseases in the same institution from 1892 to 1912. He was one of the founders of the San Francisco Polyclinic and served as its first dermatologist, from 1892 to 1900. He was a member and at one time president (1910) of the American Dermatological Association. He belonged to various other scientific organizations, including the American Medical Association. He had been a member of the University Club and the San Francisco Golf Club for many years.

Dr. Montgomery had enjoyed a large, active practice for fifty-five years, and the trip to Ecuador was only one of many journeys that took him and his wife to distant parts of the world. Only a few years ago (at the age of 78) with Mrs. Montgomery he made a round trip by clipper plane to China. They also made a side trip far into the interior in a single-motored plane. While in Brazil (1910) he heard of Ehrlich's discovery. He then hurried to Europe and secured some arsphenamine,

which he sent to the University of California Medical School, the first arsphenamine to be used in America. Dr. Montgomery was one of the first men in the West to have an x-ray machine and radium. Always abreast of the times, he was one of the outstanding dermatologists,

DOUGLASS W. MONTGOMERY, M.D.
1859–1941

the dean of dermatology in the West. As a consultant, he always gave most helpful advice, and other dermatologists often took their problems to him.

On Dec. 14, 1937, at a special meeting, the San Francisco County Medical Society honored him on his fifty-second year of continuous practice in San Francisco. He was then presented with the following engraved resolution:

Whereas, our friend and colleague, Douglass W. Montgomery, has not only continuously and successfully practiced medicine in this city for fifty years, but is still energetically pursuing that art according to the ethics and oath of Hippocrates; be it Resolved that his friends, the members of the San Francisco County Medical Society, herein acknowledge that unusual accomplishment and offer to him their heartfelt felicitations and sincere good wishes for continued health and happiness.

Through the four years following this meeting he continued leading an active life, being at his office daily from 10 in the morning till late in the afternoon, where he was kept busy by his many devoted patients. With all this he continued to write for medical literature, his contributions being of fascinating interest from both the scientific and the literary standpoint. During his long useful life his contributions to literature were many, too numerous to be listed here. All of his friends and acquaintances have shared the keen interest and pleasure of hearing him recount his experiences and observations. He was popular at any gathering and entertained every one with his witty observations and, often, his Scotch stories.

Douglass Montgomery sought no public office and did not care for politics. Medical politics never interested him, as he preferred to devote his activities to professional work. Once when asked what his favorite amusements were, he replied, "Observing my fellow beings."

During the twenty years of his professorship in the department of dermatology of the University of California, he had thousands of students who never forgot him and who remembered with gratitude the excellent instruction he had given them. His papers and discussions at scientific meetings always were most interesting and instructive. In dermatology, as in other fields, he had innumerable friends in many countries. It can be said that he was one of the best known dermatologists here and abroad. He was a cultured gentleman, of keen wit and fine powers of observation. These traits together with his delightful personality and youthful spirit made him an unforgettable character.

HARRY E. ALDERSON, M.D.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

RITTER'S DISEASE: REPORT OF A CASE IN WHICH RECOVERY OCCURRED. JOSEPH SCHWARTZMAN, DAVID DRAGUTSKY and GEORGE ROOK, Am. J. Dis. Child. **62**:352 (Aug.) 1941.

The authors report a case of Ritter's disease in which vitamin therapy, preeminently the administration of riboflavin, produced a rapid and successful result. From this 1 case they assume that this disease may be due to a primary vitamin deficiency on which is superimposed a secondary bacterial infection.

SUCCESSFUL TREATMENT OF NOMA WITH SOLUTION OF FORMALDEHYDE: REPORT OF SIX ADDITIONAL CASES. SIM I. MCMILLEN, Am. J. Dis. Child. **62**:590 (Sept.) 1941.

In 1935 the author reported successful therapy in a case of noma with solution of formaldehyde (British Pharmacopeia). The present article recounts the use of this remedy in 6 consecutive cases without 1 death. Sulfanilamide and sulfapyridine were without value.

PRIMARY INOCULATION TUBERCULOSIS OF THE SKIN: ITS OCCURRENCE IN A FOUR YEAR OLD CHILD. RONALD B. SCOTT, Am. J. Dis. Child. **62**:596 (Sept.) 1941.

This is a report of a case of a primary tuberculous complex involving the skin of a 4 year old Negro boy. The primary lesion followed an abrasion of the skin over the right knee cap. Draining sinuses developed from the involved inguinal lymph nodes in the right groin. The primary lesion over the right knee took on the clinical appearance of tuberculosis verrucosa cutis.

ASSOCIATED FACIAL HEMANGIOMA AND INTRACRANIAL LESION (WEBER-DIMITRI DISEASE). HARRY J. COHEN and MAURICE N. KAY, Am. J. Dis. Child. **62**:606 (Sept.) 1941.

A case is reported in which a 10 year old Negro girl had the following conditions: (1) a port wine nevus on the right side of the face, (2) calcification of the occipital lobe of the cerebrum on the right side, (3) convulsive seizures involving the side opposite the cerebral lesions and (4) visual disturbances. Roentgenograms of the skull revealed the calcified area in the right occipital lobe.

NELSON PAUL ANDERSON, Los Angeles.

THE EFFECT OF SYPHILIS AND ITS TREATMENT ON THE INCIDENCE OF TOXEMIA OF PREGNANCY. CHARLES H. PECKHAM, Am. J. Syph., Gonor. & Ven. Dis. **25**:280 (May) 1941.

The relation of syphilis and toxemia of pregnancy as observed in a series of 13,742 consecutive deliveries is reported. The incidence of toxemia of pregnancy was found to be somewhat lower in syphilitic than in nonsyphilitic patients. As a result of this study, Peckham concluded that antisyphilitic treatment administered to pregnant syphilitic women does not increase the incidence of toxemia of pregnancy. He compared his figures with those of a general clinic population.

STUDIES OF THE TRANSMISSIBILITY OF SYPHILIS: THE INFECTIOUSNESS OF THE VAGINAL SECRETIONS AND MENSTRUAL BLOOD OF SYPHILITIC WOMEN. HARRY PARISER, Am. J. Syph., Gonor. & Ven. Dis. **25**:339 (May) 1941.

A total of 30 syphilitic women, only 1 of whom had had previous treatment (three and one-half years prior to examination), were subjected to a study of

vaginal secretions. Seventy-six per cent had early syphilis and 24 per cent late syphilis. Dark field examination and animal inoculations were made of these secretions. Pariser concluded that virulent spirochetes are discharged by a syphilitic woman into the vagina in the presence of local lesions early or chronologically "late" (more than four years' duration) in the course of the disease as a relapsing phenomenon. The physiologic secretions are not infectious, but infectiousness depends entirely on the presence of local lesions.

REUTER, Milwaukee.

A NEW TREATMENT FOR BURNS: PRELIMINARY REPORT. KENNETH L. PICKRELL, Bull. Johns Hopkins Hosp. **69**:217 (Aug.) 1941.

This article deals with the use of sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) in the treatment of burns. For all extensive burns, shock is combated, cultures are taken and sterile precautions are used. The burned areas are sprayed with 3 per cent sulfadiazine in 8 per cent triethanolamine with an atomizer. This is done every hour during the first day, every two hours the second day, every three hours the third day and every four hours the fourth day. Further technical details are given. The method has been used for 115 patients suffering from burns. The results have been very gratifying and superior both to the tannic acid method of Davidson and to the aniline dye method of Aldrich. The method is relatively simple, and the treatment relieves pain and prevents infection. Dermatologists who serve with the armed forces or with emergency disaster groups should be acquainted with this method.

NELSON PAUL ANDERSON, Los Angeles.

A CASE OF DISSEMINATED BLASTOMYCOSIS. L. J. SOLWAY, M. KOHAN and H. G. PRITZKER, Canad. M. A. J. **41**:331 (Oct.) 1939.

Solway, Kohan and Pritzker report the case of an Italian fruit peddler aged 48 who complained of weakness, shortness of breath on exertion and loss of weight. The only cutaneous manifestation was an insignificant pustular lesion under the left ala nasi; in material from this, budding yeast cells were demonstrated, and a biopsy and cultures verified the diagnosis of blastomycosis. Physical examination revealed involvement of the lungs, and invasion of other organs was suspected. There was shown to be similarity to turberculosis both in the clinical findings and in the course of the disease. Sulfanilamide was administered without success. The course of the disease was gradually downward and the patient died with terminal bronchopneumonia. The autopsy revealed changes in the lungs, epididymis, spleen, spinal cord, prostate and liver. The liver and spleen showed chronic hepatitis and splenitis of a nonspecific type; in the other organs definite lesions of blastomycosis were demonstrated. The authors state that their case is the third on record in which the spinal cord was shown to be involved.

BOECK'S DISEASE (SARCOID): ITS CLINICAL GROUPS AND DIAGNOSIS. J. H. PALMER, Canad. M. A. J. **42**:11 (July) 1940.

Palmer reviews the subject of sarcoidosis, emphasizing the salient features, many of which are hidden. He points out that the disease process may be found in any organ or tissue, that the prognosis is usually favorable as to the eventual outcome and that the diagnosis while often obvious may at times rest on histologic grounds. He also emphasizes that while the roentgenologic appearance of the lungs or bones of the hands may usually be considered typical, in some instances the roentgen rays may not disclose any bony involvement. The reaction to tuberculin is often negative. The cutaneous lesions may be either specific dermatoses, including tumors and Schaumann's erythroderma (a nonitchy scaly rash affecting the legs), or nonspecific eruptions, such as prurigo and urticaria.

SYPHILIS AS A CANADIAN PROBLEM. F. E. CORMIA, Canad. M. A. J. **42**:476 (May) 1940.

From a study of available sources Cormia concludes that 5 per cent of the population of Canada have syphilis. He estimates that the death rate for syphilis approaches that for tuberculosis in Canada. There was evidence that the number of new cases of syphilis increased until about 1920 and became stationary until 1930, with a decrease since then. Cormia makes a plea for additional educational measures for both physicians and laymen with more binding laws regarding premarital serologic tests and examination of pregnant women, as well as compulsory treatment in cases of infectious syphilis.

THE VALUE OF ELIMINATION DIETS IN THE TREATMENT OF INFANTILE ECZEMA. A. R. BIRT, Canad. M. A. J. **42**:520 (Dec.) 1940.

From experience in 198 cases of infantile eczema, Birt believes that the use of elimination diets combined with suitable local treatment is more efficacious than local therapy alone. He outlines in detail the diets suitable for use in infancy. Egg was the commonest offender. Tomato was next, followed in descending order by orange, milk, fish, oatmeal and cod liver oil. Many other foods were occasionally indicted. Wool and soap were the commonest local irritants. Of 54 patients who had had infantile eczema five to ten years previously, nearly 25 per cent had some atopic disorder and another 25 per cent had contact dermatitis.

NAIL POLISH DERMATITIS. J. F. BURGESS, Canad. M. A. J. **42**:544 (Dec.) 1940.

Burgess records the findings in 10 cases of dermatitis about the face and neck in which positive reactions were obtained from patch tests with nail polish and in which a clinical cure resulted when use of the polish was discontinued. In 1 case pruritus ani was simultaneously relieved. Burgess also stated that in other cases in which relief followed the removal of nail polish, patch tests did not verify the diagnosis; if reliance on the test had been total, an error would have occurred.

THE TREATMENT OF LICHEN PLANUS WITH VITAMIN B COMPLEX. J. F. BURGESS, Canad. M. A. J. **43**:120 (Feb.) 1941.

From a consideration of its use in 15 cases of lichen planus, Burgess concludes that vitamin B complex is of therapeutic value in the acute stages, exerting almost, at times, a specific effect. The effect is not so pronounced on chronic lichen planus. He was unable to evaluate the worth of the individual components of the B complex.

AN ERUPTION CLOSELY RESEMBLING LICHEN PLANUS DUE TO WHEAT GERM. A. H. NEWMAN, Canad. M. A. J. **43**:175 (Feb.) 1941.

Newman reports the case of a man aged 47 in whom an eruption developed closely resembling lichen planus, the individual lesions being angular, umbilicated and striated; they were not violaceous but reddish. The eruption disappeared six weeks after the ingestion of wheat germ was discontinued. Flare-ups occurred when wheat germ and later wheat germ oil were administered, but no cutaneous rash followed the ingestion of fresh brewers' yeast. LEWIS, New York.

STUDY ON REAGIN CONTENT OF SPINAL FLUID. MCKINLEY LONDON, J. Allergy **12**:244 (March) 1941.

In the spinal fluid of 6 atopic persons sensitive to ragweed and of 1 sensitive to grasses the author was unable to demonstrate reagins, even when these were present in comparatively high concentrations in the blood. Agglutinins, lysins and other antibodies which show a comparatively ready diffusibility may traverse

the choroid plexus or meninges. The atopic reagin, however, has a strong affinity for fixed tissue and evinces a refractoriness toward passage through an anatomic membrane.

CUTANEOUS AND SYSTEMIC REACTIONS OBSERVED DURING ORAL POISON IVY THERAPY. BEDFORD SHELMIRE, J. Allergy **12**:252 (March) 1941.

Approximately 1 of every 4 persons living in a district infested with poison ivy is clinically sensitive to the ivy vine or shrub. Two types of ivy dermatitis exist, the irritative and the allergic. The milky juice of the poison ivy plant is escharotic, and all persons who come in contact with this sap have a subsequent dermatitis. The author observed many instances of the irritative type of ivy dermatitis in persons who were not allergic to the plant, i. e., persons who failed to react to a 1 : 10 solution of the ivy in acetone, the bruised leaf and plant meal on patch test.

In a relatively high percentage of the cases ivy dermatitis does not result from direct contact with the plant but follows indirect contact with such intermediary contaminated objects as hands of other persons, pets, golf clubs, shoes and other types of clothing and garden and farm tools. The belief that one may have an ivy dermatitis by merely going into the vicinity of the plant is erroneous. The author repeatedly took extremely sensitive persons to within a few feet of the plant and gently stroked their forearms with uninjured leafy branches. In not a single instance did ivy dermatitis develop.

In the author's opinion the intramuscular injection or oral administration of weak dilutions of ivy oleoresin does not benefit an existing ivy eruption. Stronger concentrations of the extract are prone to exaggerate the dermatitis.

Approximately 40 ivy-sensitive persons received either shock doses (large) of or prolonged fractional oral therapy with an ivy oleoresin in corn oil. Reactions of the skin and mucous membrane, especially pruritus ani, developed in many of the patients, particularly following a period of shock therapy. Oral therapy resulted in hyposensitization, yet desensitization did not occur. Massive oral doses, given experimentally and not recommended for routine oral treatment, were otherwise harmless, as blood counts, urine, readings of blood pressure and results of general physical examination remained normal throughout the treatment period.

STUDIES ON BLOOD HISTAMINE IN CASES OF ALLERGY: III. THE EFFECT OF THE ADMINISTRATION OF HISTAMINASE ON THE SYMPTOMS AND THE HISTAMINE CONTENT OF THE BLOOD IN PATIENTS WITH ALLERGY. BRAM ROSE, J. Allergy **12**:441 (July) 1941.

The histamine content of the blood and symptoms of 36 patients with allergic disease have been observed by the author during the administration of histaminase both orally and intramuscularly. There were 15 cases of urticaria, 11 of asthma, 5 of vasomotor rhinitis, 3 of angioneurotic edema and 1 of eczema. The daily oral dose was from 30 to 150 units; the intramuscular dose was from 1 to 8 units.

No effect on the histamine content of the blood was noted in all patients following or during the administration of histaminase. In 2 patients with urticaria and in 1 each with asthma and vasomotor rhinitis, questionable improvement in symptoms was observed. In 4 of the 7 patients treated by the intramuscular injection of histaminase, reactions, consisting of swelling, redness and tenderness at the site of injection, were observed.

ORAL IMMUNIZATION FOR POISON IVY DERMATITIS. LOUIS ZISSERMAN, J. Allergy **12**:474 (July) 1941.

The author attempted to immunize 100 boy scouts and their adult leaders several months before their going to camp, by the oral administration of enteric-coated tablets containing 0.01 mg. of an ether-soluble extract of the poison ivy plant. The dosage was as follows: 1 tablet daily for seven doses and then 1 twice

weekly. This therapy was continued to and throughout the stay in camp. The total number of tablets taken varied from 15 to 30 per person.

The results were unsatisfactory, as there was practically the same incidence of poison ivy dermatitis among the treated persons as among a large group of controls.

MENDELSOHN, New York.

ERYTHEMA MULTIFORME BULLOSUM WITH INVOLVEMENT OF THE MUCOUS MEMBRANES OF THE EYES AND MOUTH (STEVENS-JOHNSON DISEASE). HARRY AGELOFF, New England J. Med. **223**:217 (Aug. 8) 1940.

The case of a 4 year old white girl is described in detail.

The patient was given a course of azosulfamide, 40 grains (2.59 Gm.) a day for nine days; the eyes were washed frequently with boric acid solution, and 1 per cent gentian violet was applied to the cutaneous lesions. Several drops of a 1:2,500 solution of metaphen was instilled into the eyes three times a day, and later butyn sulfate-metaphen ointment was used. Eighteen hundred milligrams of vitamin B complex and 25 mg. of ascorbic acid were administered daily. Sedatives were given liberally. The child recovered in three weeks, and on discharge faintly pigmented areas were the only remaining evidences of the lesion.

Stevens and Johnson, in 1922, described this syndrome as that of an eruptive fever with stomatitis and ophthalmia. In the 9 cases described only 2 patients escaped total blindness, and these remained partially blind.

In only 1 of all the cases described, exclusive of the author's, did the disease occur in a girl; the patients ranged in age from 22 months to 16 years.

GENGENBACH, Denver. [AM. J. DIS. CHILD.]

SKIN MANIFESTATIONS DUE TO SULFANILAMIDE AND ITS DERIVATIVES. A. M. GREENWOOD, New England J. Med. **224**:237 (Feb. 6) 1941.

Greenwood states that there is no single rash characteristic of reactions to sulfanilamide or its derivatives. They are of a multiform character. The majority, however, are maculopapular and not generalized; they are accompanied by fever and pruritus, and in many cases they are of almost maroon color. They are more likely to appear in areas exposed to sunlight.

IS THERE A COMMON DENOMINATOR IN SCLERODERMA, DERMATOMYOSITIS, DISSEMINATED LUPUS ERYTHEMATOSUS, THE LIBMAN-SACKS SYNDROME AND POLYARTERITIS NODOSA? B. M. BANKS, New England J. Med. **225**:433, 1941.

Banks reports a case of scleroderma in which autopsy revealed pathologic changes in the arterioles and in the connective tissue that were similar to those in previously reported cases of scleroderma. The report is followed by a discussion of the ill defined symptoms of dermatomyositis, disseminated lupus erythematosus, the Libman-Sacks syndrome and polyarteritis nodosa, their interrelations and similarities. The etiologic agents causing the vascular changes are obscure. There are no pathognomonic pathologic changes in systemic lupus erythematosus. Frequently a condition diagnosed as typical of one disease by careful clinicians then progresses and typical or classic clinical and histologic features of another develop. A diagnosis in the early phases must be regarded as only tentative. No more clarifying conclusion is offered.

RONCHESE, Providence, R. I.

EPILOIA. L. M. QUILL and E. C. MARTING, Surgery **9**:581 (April) 1941.

Quill and Marting describe the syndrome of epiloia observed in 7 persons of three generations. Although the mother of the first and seventh patients (the grandmother of the other 5 patients) was not examined clinically, the history of epileptic seizures, adenoma sebaceum and tumors of the nail bed makes the diagnosis of epiloia a valid presumption. If this is granted, the study reveals direct passage of the disease through three generations. The study discloses that if the

patient with epiloia lives through puberty and is capable of mating transmission of the disease is possible. The reason for so few examples of transmission lies in the fact that the average affected patient is so mentally and physically incapacitated at puberty that marriage and mating do not occur. Study of the family tree discloses that 1 daughter (case 1) of the patient with the original epiloia transmitted the disease in all its intensity to all 4 of her children who lived to puberty, whereas the other daughter (case 7) with signs of the disease apparently did not pass it on to her 2 older children. There is no evidence of the disease in the other 2 children of the patient with the original epiloia. Neither was the condition found in their children. This suggests that the disease is not recessive but rather incompletely dominant. The tumors of the nail bed, usually an uncommon accompaniment, are of particular interest because of their presence in all 7 cases. The presumption here is that epiloia is transmitted, even in its minute details. The direct transmission of the disease from parent to offspring through three generations proves that the syndrome is hereditary, i. e., genotypical, as suggested by Fabing.

J. A. M. A.

"Allowable" Claims for Vitamin A Deficiency: The Relation of Visual Defects and Skin Lesions. D. Fitzgerald Moore, J. Trop. Med. **44**:47 (April 15) 1941.

Several observers have claimed that phrynoderma is related to vitamin A deficiency. No one denies that xerophthalmia is due to a deficiency of this vitamin, although cases of severe phrynoderma of several weeks' duration have been observed in which there was no loss of night vision. Thus if the claim is acceptable that phrynoderma is a manifestation of vitamin deficiency, the author believes that it is difficult to assume that night blindness is an early, or even invariable, symptom of avitaminosis A.

Phrynoderma has been noted in scurvy, and in experimental scurvy the characteristic follicular hyperkeratoses appeared even though the patient was receiving adequate amounts of vitamin A.

The author states that there still remains a great deal of uncertainty concerning this question.

Tropical Ulcer of the Toes. Earle K. Vigors, J. Trop. Med. **44**:88 (July 15) 1941.

Although the majority of tropical ulcers occur on the lower extremities, they seem to have been inadequately described when they occur on the toes. The toe itself, the interdigital clefts or the nail beds may be affected. While in most locations they extend no deeper than the deep fascia, the tendon sheaths or joint cavities of the toes may be involved. Treatment consists in rest and a diet rich in thiamine (vitamin B_1). The sores are cleansed with a 1:150 solution of copper sulfate, and cod liver oil or whale oil preparations are used to promote epithelization. Sulfapyridine is of value in the early stages but disappointing in conditions of long duration. Lesions on the toes usually occur in barefooted natives, while those between the toes occur almost exclusively in shoe-wearing Europeans, Creoles or Chinese. The nail beds may be involved by an ulcer on the dorsum of the toe extending around the lateral margin of the nail or by one commencing on the distal end of the toe and extending under the ail.

The Treatment of Wounds Caused by Wild Animals. L. F. S. de Hartogh, J. Trop. Med. **44**:112 (Sept. 1) 1941.

In the Netherland East Indies wounds caused by crocodiles are relatively frequent, and occasionally wounds made by the tusks of boars are seen. In the case of crocodiles, an adult can nearly always escape from an attack in shallow water if he can reach the head of the alligator and press on its eyes, whereupon the beast will instantly let go his prey and run away. In case of bite, the wounds are

usually open and irregular with dirty gray tissue at the bottom, seldom suppurating, atonic and without tendency to heal spontaneously. Neither excision nor treatment with compresses of sodium permanganate and acriflavine hydrochloride produced striking results. Finally the author tried strong solutions of boric acid, which proved highly successful. The wound was first cleaned with a 3 per cent solution of hydrogen peroxide, washed with 1 : 10,000 solution of mercury bichloride, lightly dried and then powdered with a thick layer of boric acid. The dressing was changed twice daily and the boric acid reapplied. In five to seven days the wounds were granulating and clean, and they were dressed only once daily during the second week. In the third week an ointment containing 2 per cent salicylic acid and 6 per cent boric acid was used. This treatment is painful for about ten minutes after the boric acid powder is applied during the first few days of treatment.

LAYMON, Minneapolis.

PINK DISEASE TREATED BY WHEAT GERM. G. FORSYTH, M. J. Australia **1**:78 (Jan. 18) 1941.

Forsyth reports 3 cases of acrodynia in which prompt cure occurred with the administration of wheat germ (bemax) in the amount of 3 ounces (89 cc.) daily.

GONCE, Madison, Wis. [AM. J. DIS. CHILD.]

STATISTICS ON THE CASES OF TUBERCULOSIS OF THE SKIN OBSERVED FROM 1929 TO 1939. A. NAVARRO MARTIN, Actas dermo-sif. **32**:301 (Jan.) 1941.

The author studied the incidence of tuberculosis of the skin in Santander, one of the northern provinces of Spain. This condition occurred in an average of 1.83 per cent of all cases of diseases of the skin. Cutaneous tuberculosis was found to occur much more frequently in women (78.8 per cent) than in men (21.2 per cent). Erythema induratum was seen in 106 women and in only 3 men. The lesions were more frequently observed in men during their first ten years and in women during their second decade. Papulonecrotic tuberculid was the form more frequently associated with other types.

In 61 cases the chest was examined. In 50.8 per cent there were signs of inactive tuberculosis of the lungs; in 24.6 per cent there were active lesions; in 6.5 per cent there was tuberculosis of the hilum, and in 3.7 per cent there were residua of pleurisy. Tuberculosis of the glands was observed in 28 out of 223 cases.

PRESENT STATUS OF THE PROPHYLAXIS OF VENEREAL DISEASES IN THE REPUBLIC OF ARGENTINA. JOSÉ J. PUENTE, Bol. Ofic. san. panam. **19**:852 (Sept.) 1940.

The law regulating the prophylaxis of venereal disease in Argentina dates from December 1936. Among many improvements this law requires that all hospitals have a service for the treatment of venereal diseases. At present there are seven hundred and nine clinics in which such diseases are treated. A uniform chart to record the treatment and a standard method of therapy were also instituted. Compulsory premarital physical examination, including a test of the blood, is limited to men. A hundred and twenty thousand posters and ninety thousand pamphlets about venereal diseases have been distributed. In order to reduce the cost of the treatments, the drugs are exempt from taxes.

The compiled statistics of nineteen clinics in Buenos Aires and of nine others in different large cities show that the incidence of chancroid increased in 1935 (more than 1,000 cases) but decreased greatly in the following years. In 1939 there were only 15 cases. The number of cases of gonorrhea also diminished. In 1934 about 1,800 cases of early syphilis were observed. In 1939 only about 700 patients were observed and treated.

CANIZARES, New York.

PSEUDOXANTHOMA ELASTICUM. TIBOR VENKEI-WLASSICS, Dermat. Wchnschr. **107**:1396 (Nov. 26) 1938.

The author reports 2 cases of pseudoxanthoma elasticum. In 1 the anal region was involved, and in the other, the inguinal folds. Neither patient had angioid streaks of the retina.

TAUSSIG, San Francisco.

CONSERVATION OF SERUM BY DRYING ON PAPER (ACCORDING TO THE METHOD OF KRIVONOSOVA) FOR THE PURPOSE OF SERODIAGNOSIS OF SYPHILIS. R. LIEBERMAN, Vestnik ven. i dermat., 1939, no. 1, p. 90.

In the Leningrad Dermato-Venerologic Institute the method of conservation of serum on paper for the purpose of serodiagnosis of syphilis has been investigated. This method was suggested by Butiagin and improved by Krivonosova. Its technic is as follows: Two drops of 0.5 cc. of the serum to be examined are placed on a piece of writing paper, which is left to dry for twenty-four hours at room temperature. The dried drops are cut out of the paper and put into a test tube, and 1 cc. of physiologic solution of sodium chloride is added. After two hours at room temperature the 2 drops of dried serum, which dissolves in the salt solution in the test tube, yield the original concentration of the serum, which may be used for Wassermann and precipitation tests. The paper is then removed from the test tube by means of a glass rod which has a small hook at the end. Two hundred serums were examined, of which 119 were from patients with syphilis and 81 from persons used as controls. The majority of serums dried on paper gave the same Wassermann and precipitation reactions as the nondried serum. The author found that it is necessary to inactivate the serum before or after drying. The dried serum should be examined before ten days has elapsed. This method has proved exceedingly valuable, for it simplifies the transportation of blood serum from distant places.

STUDIES ON THE ZOSTER VIRUS. O. I. KIN, Jap. J. Dermat. & Urol. **47**:39 (Feb.) 1940.

The author states the belief that he has succeeded in the transmission of herpes zoster to rabbits by injecting the contents of the vesicles into the cornea and testes. The experiments led to the following conclusions:

1. Serum of convalescents contains a specific antibody which seems to neutralize the virulence of the inoculated virus.

2. The virus is filtrable and passes the Berkefeld N filter. The animal testicular tissue inoculated with this virus can conserve the virulence of the virus, when mixed with equal parts of glycerin and physiologic solution of sodium chloride, for two to three months or occasionally for as long as nine months.

Herpes zoster virus may be cultured on the chorioallantoic membrane of the chick embryo like other filtrable viruses.

BLOOM, New York.

TELANGIECTASIA MACULARIS ERUPTIVA PERSTANS: A TELANGIECTACTIC AND RELATIVELY PIGMENTLESS VARIETY OF URTICARIA PIGMENTOSA OF ADULTS. F. PARKES WEBER and H. RAST, Acta dermat.-venereol. **16**:216 (July) 1935.

This condition is characterized by a more or less generalized eruption composed of persistent red or purple telangiectatic macules. There is a tendency to confluence, with the production of irregular patches. Purpuric lesions are absent. The eruption may appear at any age; usually it occurs in adult life, and it is often present in obese women. The author cites ten cases of telangiectasia macularis eruptiva perstans mentioned in the literature and describes his own case. The relationship of this disease to urticaria pigmentosa is discussed.

ASTRACHAN, New York.

MELANOBLASTOSIS CUTIS LINEARIS S. SYSTEMATISATA. W. L. L. CAROL and D. J. H. BOUR, Maandschr. v. kindergeneesk. **9**:461 (Sept.) 1940.

A case of incontinentia pigmenti in a girl of 9 months is reported. After careful consideration the name of melanoblastosis cutis linearis s. systematisata was given to the disease. In some cells of the corium, which on other grounds were already regarded as melanoblasts, the dopa reaction (Bloch) was found to be positive. Other names which had been given to the condition were rejected by the authors. Typically in this condition at birth, shortly after birth or when the child is a few years old there appear pigmented spots in characteristic linear extension. The spots have a peculiar irregular form, are light to dark brown and are found especially on the trunk and extremities.

VAN CREVELD, Amsterdam, Netherlands. [AM. J. DIS. CHILD.]

Society Transactions

MANHATTAN DERMATOLOGIC SOCIETY

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Chronic, Exudative, Discoid and Lichenoid Dermatitis. Presented by DR. HERMAN SHARLIT.

B. W., a white man aged 37, first consulted me in August 1935. He was then and still is a silk buyer, which means that he is engaged in handling dyed silk. This eruption was identical with the condition first described at clinical meetings by Dr. Rosen and subsequently by Dr. Sulzberger and others as "chronic, exudative, discoid and lichenoid dermatosis" and later by Dr. Cannon as "allergic dermatitis simulating lymphoblastoma." The essential clinical characteristic presented by the patient in 1935 was a generalized eruption, including the genitals, which was eczematoid. The condition was further characterized by severe itching, areas of lichenification, discoid lesions and a generalized adenopathy. The eruption first appeared on the dorsa of the feet and was thought to be caused by sensitization to the dyes in silk. The Labor Board acquiesced in this opinion, and the condition was regarded as compensable under the law.

This patient was under my care from August 1935 to October 1936, including many weeks of hospitalization. At the end of this time the eruption had cleared fairly well. However, during this whole interval, and particularly in the later months when the lesions were disappearing, recurrent urticarial lesions developed, from which tendency the patient has never recovered. The patient discovered that when he had urticaria he was relatively free of other cutaneous lesions, and he began to look on the urticaria as a good sign. He has persisted in the same type of occupation all these years and was relatively free of any eruption until Aug. 4, 1941. He then presented an eczema of the dorsa of the feet, with changes of the skin about the toes and soles, suggestive of dermatophytosis. This became rapidly generalized, with repetition of the episode of 1935.

The eruption is now definitely regressing and in several respects has been less severe than his original attack, particularly in that no edema of the legs or chills have developed and the adenopathy is not as great as during his first attack.

It is difficult to establish the mechanism of evolution in this dermatosis and also the cause. The patient is presented in the hope that assistance may be obtained in an endeavor to ascertain the cause and proper therapy.

DISCUSSION

DR. ISADORE ROSEN: I think that the condition belongs to the group of chronic, exudative and discoid dermatitides. The lesions are sharply outlined, and some are infiltrated and vesicular. This disease is occasionally mistaken for dermatitis herpetiformis or some other chronic toxic eruption. It is definitely known that the picture changes from week to week. When the eruption first appears it often simulates dermatitis venenata or a severe allergic dermatitis. After a few weeks it may simulate lichen planus, psoriasis or even mycosis fungoides. Except for an increase in eosinophils, which is present in all cases of this kind at the height of the disease, and a generalized adenopathy, examinations usually show no abnormalities. After a while the condition becomes stationary with occasional periods of exacerbations and remissions. The best therapeutic results have been obtained

in a series of my patients who have been sent to San Antonio, Texas; the warm dry climate has been beneficial to all of them. Some of the patients who stayed there two or more years have returned and remained well.

DR. E. WILLIAM ABRAMOWITZ: I have had a few patients who could not afford to go to a high dry climate but who apparently recovered. One patient was observed for fifteen years or more. That patient had attacks which lasted sometimes as long as three or four years, with periods of remissions as long as five or six years. Nothing in particular was of any help. He just recovered from an attack recently that lasted about one and a half years. He had characteristic lesions of this disease.

DR. HERMAN SHARLIT: I want to call attention to a famous case of Dr. Fanburg's in Newark. The patient was a physician who traveled from one dermatologist to another trying to find out what was wrong with him, and Dr. Fanburg realized that he had the disease under discussion. He definitely established that the whole trouble was due to moth ball products. When the patient rid himself of these he became perfectly well and stayed well. These are sensitization reactions and are difficult to analyze; therefore it is hard to prescribe therapy that is effective. When this man first came to me in 1935 I thought the eruption was due to handling silk, and his history made me feel that I was entitled to this judgment. However, the patient refuses to believe it is due to silk. From this case and from others that I have had, I am convinced that such a condition is dermatitis venenata, no matter what the manifestations are clinically.

Dermatophytosis of the Feet with Dermatophytid of the Hands. Presented by DR. HERMAN SHARLIT.

J. L., a man aged 43, first presented himself in April 1941 with eczema and vesiculation about the toes and soles and an eruption of noninflammatory vesicles of both palms. The clinical diagnosis was dermatophytosis of the feet and dermatophytid of the hands. Treatment was applied to the feet, and the hands were untreated. Scrapings from the feet showed tinea. Within three weeks the clear palmar vesicles disappeared and gave place to minute pustules. Soon thereafter the appearance of the feet changed decidedly. The soles became studded with pustules, as did the sides of the feet, particularly on the inner borders. Furthermore, the skin became scaly and red. The lesions of the feet are definitely but slowly responding to treatment.

At present there are few lesions of the palms but pustules continue to erupt regularly thereon. The patient is presented because now the eruption appears strikingly similar to other conditions that have been called pustular psoriasis.

DISCUSSION

DR. GEORGE M. LEWIS: It would be interesting to know the results of the trichophytin test and also the results of culture. If the eruption is a fungous infection it is most unusual. Clinically it has the appearance of pustular psoriasis. If the reaction to a trichophytin test had been strongly positive and Trichophyton gypseum or some other skin-sensitizing fungus had been isolated from the feet, the evidence would have been more in favor of an unusual mycosis. In the absence of these signs the diagnosis will still be open to question.

DR. DAVID BLOOM: Clinically this eruption looks like pustular psoriasis. In order to prove it to be dermatophytosis Dr. Sharlit will have to find the fungi in the plantar lesions.

DR. ANTHONY C. CIPOLLARO: I do not think that this clinical picture is unusual. I think that Dr. Sharlit's diagnosis is correct, namely, that the condition is dermatophytosis plus a secondary inflammatory process. The pustules are not those of pustular psoriasis but are of pyogenic origin. In my opinion this eruption has no resemblance to pustular psoriasis or to pustular bacterid.

DR. MAURICE J. COSTELLO: I agree with those who think the patient has pustular psoriasis. It fits in well with the proved examples that I have seen. The resistance to treatment helps to make the diagnosis.

DR. ISADORE ROSEN: I do not doubt the microscopic diagnosis, but the picture presented is unusual. The patient has a definite hyperhidrosis palmaris et plantaris. The erythematous eruption extending upward from the dorsa of the feet indicates profuse sweating. Hyperhidrosis may be associated with secondary infections. This patient does not present the type of pustule seen in psoriasis. It is superficial and covered with a thin epidermis, as in Bockhart's impetigo. I believe that the patient has two conditions, an old dermatophytosis and a superimposed staphylococcic infection.

For therapy I recommend baths in warm permanganate solution for three or more days. If the condition responds to this treatment, it certainly is not pustular psoriasis, because this disease is resistant to all types of therapy.

DR. FRED WISE: The clinical appearance is that of advanced hyperhidrosis.

DR. HERMAN SHARLIT: At the onset the patient had eczematized lesions on the feet, blisters on the soles and heels and a myriad of noninflammatory vesicles on the hands. I never saw a more classic picture of dermatophytosis with dermatophytid of the hands. Within three weeks the whole picture changed. The large blisters disappeared, and then tiny superficial pustules developed on the palms and soles. When the blisters and eczematization disappeared, an erythematous and scaly condition began to appear on the borders of the feet, and the soles became loaded with pustules; the condition looked like what has been generally accepted as pustular psoriasis. In most of the cases, however, how the lesions started is not known. But in this case the condition unquestionably started as tinea, and it is hard to believe that coincidentally there was another disease. All my judgments are purely clinical. I think the best establishment of the diagnosis will be when this man is cured. I think the amount of sweating tonight is purely psychic. I have seen him many times, and I never saw him sweat so much.

A Case for Diagnosis (Epidermolysis Bullosa?). Presented by DR. WILBERT SACHS.

D. P., aged 15, and his sister, F. P., aged 9 years, presented themselves with bullae on the feet. A brother aged 26 also has this dermatosis. Another brother and a sister, as well as the mother, are free of lesions. The father had a similar eruption, which is supposed to have disappeared at the age of 32. On the father's side, three cousins and two children of one of them all have a similar eruption. The grandparents have never been known to have had this condition.

In all the patients mentioned the eruption began as soon as they were able to walk. In none has the eruption ever spontaneously disappeared with the exception of that alleged to have occurred in the father. The bullae make their appearance with the onset of the warm weather, and they disappear in the winter. The patients complain of pain, especially on walking, and occasional itching. In these 2 patients the toe nails are thickened and opaque and appear moth eaten.

Cultures of material from the lesions showed no growth.

Microscopic examination revealed an intraepidermic bullous lesion but not characteristic of epidermolysis bullosa.

DISCUSSION

DR. PERRY SACHS (by invitation): I have observed, at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, a similar case, that of a boy aged 10 years. He likewise gave a history of a bullous eruption appearing with the onset of walking and the presence of lesions only in warm weather. However, there was no familial history of such a dermatosis. Repeated smears, cultures and trichophytin tests did not reveal a fungus. Various forms of local therapy were of no value.

DR. DAVID BLOOM: These cases are more frequent than one supposes. They are usually overlooked, or the nature of the disturbance is not recognized. Of practical importance is the differentiation of this simple type of epidermolysis bullosa, which is transmitted according to the dominant mode of inheritance, from the dystrophic type, which is inherited according to the recessive mode. In the dominant type half of the children are expected to become affected, while in the recessive type there is only a slight chance that any of the children will manifest the abnormality. I believe that the presenter will do the right thing in revising his pathologic conception of epidermolysis bullosa. This is the second time that Dr. W. Sachs has hesitated to make the diagnosis of epidermolysis bullosa because the bulla was in the epidermis. In the simple type of epidermolysis bullosa the bulla may be very superficially located.

DR. E. WILLIAM ABRAMOWITZ: Clinically this condition appears to be the simple type of epidermolysis bullosa.

DR. WILBERT SACHS: Is it common for epidermolysis bullosa to disappear spontaneously in the winter in so many patients?

DR. HERMAN SHARLIT: There are all degrees of variations in these minor conditions. Some patients have to do a lot of walking to bring out the bullae. I think that in view of the family history one can ignore the biopsy and make the diagnosis from the clinical appearance.

DR. WILBERT SACHS: The fact that epidermolysis bullosa was originally called acantholysis bullosa shows that the bullae may occur in the epidermis. However, not all epidermic bullous lesions occurring in the epidermis are epidermolysis bullosa.

A Case for Diagnosis (Erythema Migrans? Necrobiosis Lipoidica?).
Presented by DR. E. WILLIAM ABRAMOWITZ.

B. J. D., a girl aged 9 years, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 10, 1941, with a lesion on the right thigh that had been present for one year. The past and family histories are unimportant.

On the posterior lower aspect of the right thigh there is a round, palm-sized, well defined, bluish plaque with a slightly raised erythematous border. The lesion is not associated with any subjective symptoms.

The Wassermann reaction of the blood was negative. The urine showed on one examination no abnormalities, but on another examination there was a trace of sugar. The total cholesterol content of the blood was 275 mg. per hundred cubic centimeters, with 180 mg. of esters, and there was 55 mg. of dextrose. The tuberculin reaction was negative with a dilution of 1:10,000.

The microscopic examination of the tissue suggested necrobiosis lipoidica.

DISCUSSION

DR. HOWARD FOX: I agree with the diagnosis of erythema migrans. Clinically the condition does not remotely suggest necrobiosis lipoidica.

DR. HERMAN SHARLIT: I cannot see how this condition looks like a lipoid dyscrasia at all. I think a section that has special staining is necessary.

DR. FRED WISE: I agree with Dr. Fox in the diagnosis of erythema migrans.

DR. ANTHONY C. CIPOLLARO: I agree that this case is one of erythema migrans.

DR. DAVID BLOOM: The pathologist suggested the diagnosis of necrobiosis lipoidica because in one area the connective tissue showed homogenization. A subsequent examination showed no deposits of fat.

DR. WILBERT SACHS: I cannot agree with the diagnosis of erythema migrans, nor do I believe that this dermatosis belongs in the erythema group. Microscopic examination revealed a deep process, in the deep part of the cutis and in the fat.

There were large cells and a suspicion of fat in the deep part of the cutis. There was also granular degeneration. Whether the condition is necrobiosis lipoidica I am not sure, but I believe that this is the more likely diagnosis. Frozen sections were made, and, while there was a suspicion, they did not show any fat.

DR. DAVID BLOOM: The diagnosis of possible necrobiosis lipoidica was made by Dr. Satenstein, who showed me the area in the section in which the connective tissue looked homogenized. He therefore suggested taking another specimen and staining it for fat.

DR. E. WILLIAM ABRAMOWITZ: I agree with all those who think this condition is erythema migrans. If it should turn out to be necrobiosis lipoidica, we will all have to revise our opinions of the clinical picture of this disease.

Tinea Capitis (Trichophyton Violaceum). Presented by DR. GEORGE M. LEWIS.

J. A., a boy aged 9 years, is presented from the New York Hospital. He has had an infection of the scalp and skin since early infancy. The disease on the scalp has resulted in partial loss of the hair in small patches scattered over the entire scalp. Numerous small stubs of hair broken off close to the scalp were noted in these patches. Some of the "black dots" were centered in pustules. There were also erythematous, crusted, gyrate and rounded lesions on the glabrous skin of the arms, legs, neck and trunk.

Cultures from both the scalp and the glabrous skin showed Trichophyton violaceum.

Previous treatment included many kinds of ointments, roentgen ray depilation and manual epilation. There are no other similar conditions in the family.

DISCUSSION

DR. MAURICE J. COSTELLO: This fungous infection is extremely resistant to treatment, often persisting beyond puberty. When I was associated with Dr. Fox he had a patient whose scalp was epilated three times in six years. One epilation should be tried; if the patient is not cured, a second epilation will probably not effect a cure.

DR. HERMAN SHARLIT: Apparently these conditions are more prevalent than one would suspect. I have a patient at Beth Israel Hospital with this condition whom I have been treating for four and a half years.

DR. E. WILLIAM ABRAMOWITZ: The only suggestion I can offer is a course of ethyl iodide inhalations.

DR. DAVID BLOOM: In regard to the involvement of the scalp, I should like to suggest estrogenic treatment.

DR. HOWARD FOX: In regard to my case of black dot ringworm which Dr. Costello mentioned, I would say that even the third epilation by roentgen rays failed to cure the disease. Incidentally, this was a complete epilation, so complete in fact that for several months I was extremely anxious about the return of the hair. I resolved never to epilate a scalp for the third time and will probably limit my treatment in the future to a single epilation.

DR. MAURICE J. COSTELLO: I wonder if Dr. Lewis could anticipate the result of a superimposed infection. Does he not occasionally see Trichophyton purpureum infections associated with the more common cutaneous fungous infections?

DR. ISADORE ROSEN: Why not try giving the patient fever therapy? It may help. It has been successful in some cases of chronic conditions in which everything else failed.

DR. GEORGE M. LEWIS: I should like to agree with Dr. Fox regarding the potential danger when a child's scalp is subjected to more than one roentgen ray epilation. A child who had undergone three epilations presented a problem in

management; there was difficulty in convincing the child's mother that a fourth treatment should not be given. In regard to the value of estrogens in the treatment of tinea capitis, the evidence is not conclusive. The only cases in which there was an apparently favorable response were those of infections in which there was a tendency to spontaneous cure. The reaction to trichophytin is negative in this patient, as in most other cases of resistant superficial fungous diseases.

Pemphigus (Senear-Usher Type). Presented by DR. DAVID BLOOM.

M. McG., an Irish woman aged 59, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 24, 1941 with an eruption of nine months' duration.

On the face, covering the nose and extending in the form of a butterfly to both cheeks, there is an erythematous crusted plaque with well defined borders. Similar plaques are seen in front of the ears, on the forehead, the scalp, the sternum and the entire back. Several flaccid bullae are present on the lower part of the back and on the hips. The patient appears in fairly good health otherwise.

On examination the urine was normal, and the Wassermann reaction of the blood was negative. A blood count revealed 3,800,000 erythrocytes and 10,500 leukocytes, with 58 per cent polymorphonuclear neutrophils, 4 per cent eosinophils, 1 per cent basophils, 3 per cent monocytes, 26 per cent lymphocytes and 8 per cent band forms. The hemoglobin content was 81 per cent. Microscopic examination of a bulla and of crusted skin showed the pathologic features of pemphigus.

DISCUSSION

DR. PAUL E. BECHET: I have noted considerable confusion in the differential diagnosis between bullous lupus erythematosus and the Senear-Usher syndrome at various dermatologic societies. Gilman (Senear-Usher Syndrome: Dermatosis Combining Features of Lupus Erythematosus and Pemphigus, ARCH. DERMAT. & SYPH. **24**:84 [July] 1931) stated that it was his belief that the Senear-Usher syndrome was a toxic dermatitis midway between lupus erythematosus disseminatus and pemphigus. Wise (*M. J. & Rec.* **134**:227, 1931) stated the belief that the syndrome was a form of disseminated lupus erythematosus. According to Sutton and Sutton (Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 341), the histologic structure in cases of this disease is that of lupus erythematosus and not that of pemphigus. Certainly the typical butterfly distribution of the lesions on the face of Dr. Bloom's patient would, if observed alone, be ascribed to the bullous type of lupus erythematosus. It is my belief that lupus erythematosus with its greatly varied symptomatology is a clinical entity due not to a single etiologic factor but to many different ones, among which may be classed a generalized toxemia of some unknown origin, which is responsible for the acute phases of the disease. In this category may be placed the Senear-Usher disease.

DR. WILBERT SACHS: In the bullous type of lupus erythematosus the histologic features of lupus erythematosus are present. In this case there are no such features.

DR. FRED WISE: A histologic section from the bat-wing-like lesion on the face would not show any sign of lupus erythematosus. It is only the location that suggests lupus. She shows no lesions remotely resembling lupus erythematosus. This condition is a peculiar type of pemphigus.

DR. DAVID BLOOM: To me the distribution of the eruption is the only feature resembling lupus erythematosus. Specimens for biopsy were taken from two different lesions; one contained a bulla, and the other was taken from a crusted plaque. Both showed the features of pemphigus and not those of lupus erythematosus.

Porokeratosis (Mibelli). Presented by Dr. Isadore Rosen.

F. M., a boy aged 16, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 24, 1941 complaining of an eruption on the neck which had been present since birth. Six years ago the band-like lesion in the middle of the neck posteriorly was treated in several areas by the desiccating monopolar current.

On the left side of the neck extending to the lower part of the ear, posteriorly, there is a streak ½ inch (1.3 cm.) wide showing slight depression in the center and lined with a keratotic border, which is raised in the form of a wall. A similar band is situated slightly to the left of the middle of the neck posteriorly. A horizontal band 2 inches (5 cm.) long extends from the upper end of this vertical streak and is located in the occipital region of the scalp. Besides these elongated lesions there are numerous lentil-sized roundish lesions, with similar depressions in the center and wall-like keratotic borders, located on the face and behind the left ear. In the occipital region of the scalp there is a crusted eruption which is being treated with ammoniated mercury ointment.

The Wassermann reaction of the blood was negative. Microscopic examination of the lesion in back of the left ear showed the pathologic histologic structure of neurodermatitis. The epidermis was moderately acanthotic with a loosely laminated horny zone. The basal cells contained pigment. The superficial blood vessels were dilated, and there was perivascular infiltration of round cells and connective tissue cells. There was some pigment in the loose connective tissue.

The patient's father has a nevus-like lesion of the right palm which extends to the wrist.

DISCUSSION

Dr. E. William Abramowitz: The condition in this case is the nearest to porokeratosis (Mibelli) that I have ever seen. I have observed very few cases, however. I had occasion to look at the slide with Dr. Satenstein the other day, and I cannot account for the absence of any of the typical findings of that disease. Another biopsy will be performed.

Dr. Howard Fox: I have encountered only 1 or 2 cases of this rare disease. I should make the diagnosis clinically from the close resemblance to illustrations in dermatologic textbooks.

Dr. Fred Wise: I agree with the diagnosis as presented. The condition seems to have all the necessary clinical features of porokeratosis appearing in the guise of a linear nevus.

Dr. David Bloom: Some reports in the literature claim familial incidence. In spite of the statement of the mother that no other member of the family is similarly affected, I shall try to examine the other members in order to ascertain the truth of that statement.

Cold Urticaria: Failure of Treatment with Histamine and Histaminase. Presented by Dr. George M. Lewis.

A. S., a housewife aged 54, whose general health had been satisfactory, came to the New York Hospital in December 1940 because of a troublesome reaction which developed when her skin was exposed to cold. The itching was intense in the skin so exposed and was followed by redness and swelling of the part. This reaction to cold has persisted for the past two years. The patient was hospitalized for study for ten days in January 1941. It was noted that after immersion in cold water, 8 to 10 C. for five minutes, the hand became swollen and red and a few wheals developed. The arm also became swollen to about halfway to the elbow. Five minutes after termination of the exposure, the face, neck and upper part of the chest became intensely flushed. The edema and itching continued throughout the day.

Treatment with histaminase, 10 units three times a day, was continued until the patient had taken 100 tablets. No improvement was noted. The patient was later given injections of histamine, beginning with 0.1 cc. of a 1:10,000 dilution and gradually increasing the dose up to 1 cc. of a 1:1,000 dilution. After thirty-seven injections, the patient stated that there was no relief in the condition following exposure to cold.

DISCUSSION

DR. MAURICE J. COSTELLO: I believe that one of the explanations for sudden drowning of otherwise healthy persons is a physical allergy of this type.

DR. HERMAN SHARLIT: Graded exposures to cold might help.

DR. E. WILLIAM ABRAMOWITZ: I think that a response could be brought out more quickly with an ethyl chloride spray. This eruption is not accepted by all as a purely allergic phenomenon. Histaminase is supposed to be effective in such cases, especially with high doses.

DR. GEORGE C. ANDREWS: In such cases alcohol should be avoided. Other allergies also should be studied. These so-called physical allergies are often dependent on other than physical causes.

Poikiloderma Atrophicans Vasculare (Jacobi). Presented by DR. DAVID BLOOM.

V. DeS., a boy aged 16, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on July 9, 1941 complaining of a generalized eruption of four years' duration. His past and family histories were essentially normal.

On the anterior aspect of the neck, in the hypochondriac regions, on the hips and buttocks and on the upper and lower extremities there are diffuse plaques of telangiectasia, which show mottling due to pigmentation, depigmentation and atrophy. There is also slight scaling. The eruption is not associated with any subjective symptoms.

The Wassermann reaction of the blood was negative, and the blood count and differential count did not reveal any abnormality. The basal metabolic rate was —6 per cent. The histologic examination showed features compatible with poikiloderma atrophicans vasculare (Jacobi).

DISCUSSION

DR. PAUL E. BECHET: In my opinion Dr. Bloom's case does not at all resemble the few proved cases of poikiloderma atrophicans vasculare which I have observed. The patches are aggregated, pale and erythematous and are covered with extensive, fine, loosely adherent scales. I have occasionally observed anomalous patches of parapsoriasis en plaques exactly similar in appearance to this dermatitis. The diagnosis of parapsoriasis en plaques should be considered.

DR. GEORGE C. ANDREWS: Parapsoriasis also entered my mind because of the small papular lesions that resemble psoriasis. However, I believe that this patient has poikiloderma—not poikiloderma atrophicans vasculare—in certain areas, especially on the elbows. I think the skin is definitely atrophic and telangiectatic. I suggest that he be studied on the basis of an endocrine condition. This is possibly a case like the ones described by Bloch, in which there is poikiloderma associated with an endocrine disturbance. Also vitamin A concentration in the blood should be determined.

DR. HOWARD FOX: From the clinical appearance as well as from the divergent opinions expressed, it is obvious that this case is most unusual. The condition is not the classic Jacobi type of poikiloderma, which is an extremely rare disease. The term poikiloderma-like lesions would be more suitable. However, this does not describe more than a part of the cutaneous changes. The patient has a dry skin with some chalky white scaling which gives the feel of a nutmeg grater. I agree with Dr. Andrews that vitamin A therapy should be tried.

DR. DAVID BLOOM: I have seen this boy on numerous occasions and never noticed the considerable scaling which he shows tonight, particularly on his back. He states definitely that he did not apply anything externally, so that one must assume that this scaling has appeared spontaneously. As hardly anything is known in regard to the cause of this clinical entity, all routine tests possible must be made, including vitamin determinations.

Sycosis Lupoides. Presented by DR. DAVID BLOOM.

H. S., a man aged 49, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Aug. 11, 1941 complaining of an eruption of eleven years' duration. The patient states that he never has received roentgen ray treatment.

On each side of the anterior aspect of the neck, there is a palm-sized atrophic area, denuded of hair and surrounded by an erythematous, nodular and pustular border. A similar lesion is present on the anterior aspect of each forearm.

Culture of the pustular border revealed Staphylococcus aureus. Other laboratory tests, including examination of the urine and a Wassermann test of the blood, gave negative results.

The patient is receiving staphylococcus vaccine by subcutaneous injection and chlorhydroxyquinoline (quinolor) ointment locally. He is also being treated for a chronic nasopharyngitis.

Experimental Therapy with Diphtheria Toxoid in Four Cases. Presented by DR. FRED WISE.

The following 4 cases are from a group of cases of diseases, including pemphigus, mycosis fungoides, generalized sarcoidosis, psoriasis, parapsoriasis, chronic recurrent discoid and exudative dermatitis, lupus erythematosus resistant to various forms of accepted therapeutic remedies and essential pruritus, in which treatment with diphtheria toxoid is being given, by Dr. John Garb, at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

CASE 1.—*Chronic eczema (mycotic?).*

M. F., an Italian aged 59, a grocer, applied for treatment on May 31, 1941, presenting lesions on the legs and complaining of severe itching of five months' duration. His father had asthma. He had originally registered on Feb. 3, 1941 and was then treated privately by a dermatologist with three exposures of roentgen rays and applications of salves. The routine laboratory tests, including mycologic examinations and cultures of material from the lesions in the groins and on the legs, gave negative results. Histologic sections examined by Drs. Satenstein and Sachs were diagnosed as chronic eczema.

Physical examination showed the patient to be in good health except for the eruption, which made him irritable and depressed. He presented symmetric, purplish red, crusted, oozing, vesicular and hemorrhagic patches on the dorsal surfaces of the hands, wrists and forearms, the nates, the inner surfaces of the thighs and the extensor surfaces and sides of the legs, ankles and feet. The patches were well marginated and rounded, and some were raised to about 0.5 cm. in the center but tapered off gradually to the level of the skin. They infiltrated the skin but moved freely with it. The lesions on the ankles and dorsal surfaces were most annoying because of pain on movement of the joints and interference with the patient's work.

He was hospitalized for a week. Treatment consisted of colloid, permanganate and tar baths and bichloride dressings alternating with various salves. Internally, he received 9 mg. of thiamine hydrochloride, 6 tablets of histaminase (torantil) a day, 3 tablets of vitamin B complex and pentobarbital sodium as a sedative at night. With these medications he received also subcutaneous injections of 4,000 international units of thiamine hydrochloride daily. There was no appreciable change in the character of the lesions and only slight relief from the itching.

On September 5 he received a subcutaneous injection in the right arm of 1 cc. of alum-precipitated diphtheria toxoid (Lederle). On September 13 the affected areas looked paler and the patient was more cheerful, stating that there was less itching. On September 25 he received the second injection of 0.5 cc. of diphtheria toxoid. He was seen again on October 8, when there was a striking improvement in the eczema. All of the patches had been undergoing rapid involution. They were flattened, dry, light in color and covered with sparse adherent scales. The large lesion on the inner surface of the thigh had entirely regressed. The only still prominent lesions were on the dorsal surfaces of the hands and ankles. The most striking effect had been on the itching, which had almost entirely subsided.

CASE 2.—*A case for diagnosis (mycosis fungoides?).*

D. K., a man aged 65, was presented before the New York Dermatological Society on March 25, 1941 for diagnosis (ARCH. DERMAT. & SYPH. **44**:770 [Oct.] 1941). The alternative diagnoses of phenolphthalein eruption, drug eruption and pemphigus were entertained. The patient has been treated since then with more roentgen ray therapy, solution of potassium arsenite U. S. P. and injections of 1 per cent sodium arsenate subcutaneously up to 28 minims (1.7 cc.) a day. This therapy was stopped because of complaints of gastrointestinal distress. The patient failed to improve. When she was seen on August 30, there were present on the scalp, face, upper part of the shoulders, back and extremities numerous bullous lesions, many of which were ruptured. There were also many flat, reddish yellow, sharply defined, slightly infiltrated, oval and discoid, scaly lesions on the trunk, varying from 1 to 3 inches (2.5 to 7.5 cm.) in diameter, clinically resembling mycosis fungoides. The latter lesions were decidedly itchy.

On September 2 1 cc. of diphtheria toxoid was injected subcutaneously in the left arm. On September 9 the patient stated that he felt much better. He had only slight itching. Most of the bullous lesions on the scalp and face had undergone involution and were covered with new epithelium. The plaques on the body were paler and smaller. There were no new blisters. On September 13 the patient showed continued improvement. The discoid lesions on the body became paler and were covered with fine scales. On September 23 regression was more pronounced. The scalp was practically healed. A second injection was then given. On October 3 he received the third and on October 12 the fourth injection of diphtheria toxoid of 0.5 cc. each. On the latter date he showed continued improvement, most of the bullous lesions on the back being dried and in the process of healing.

CASE 3.—*Pemphigus.*

I. H., a white woman aged 60, on May 15, 1941 had lesions on the scalp and buttocks of one year's duration and complained of continuous shooting pains on the top of her head.

The entire two thirds of the right half of the scalp, extending from the middle of the right side of the forehead to about 1 inch (2.5 cm.) in front of the lambda and laterally along the hair margin, was soft, mushy, hemorrhagic and covered with a greenish, waxy, adherent exudate. There was a partial alopecia, and the remaining hairs were sticky and held down by this mucilaginous secretion. The entire area was uniformly involved except at the posterior parietal region, which was crusted. The areas affected were tender and bled freely with the slightest irritation, the tissue being friable and only loosely attached to the calvaria. There was a similar area on the intergluteal fold, 4 by 2 cm. wide. A histologic section taken from the intergluteal fold showed "dermatitis vegetans; might fit in with pemphigus vegetans."

The patient was treated with dressings of mercury bichloride, 1:3,000, solution of aluminum acetate, 1:10, and emollient salves to the scalp and 3 per cent ammoniated mercury to the lesion in the intergluteal fold. She also took 1 tablet of cortalex with 15 grains (1 Gm.) of salt three times a day for three months

(each tablet contained 5 Gm. of adrenal gland extract and 15 mg. of ascorbic acid). The patient continued to use all of these medications without any noticeable improvement.

On September 2 1 cc. of diphtheria toxoid (alum precipitated) was injected subcutaneously in the left arm. On September 4 the patient stated that the pains in her head were about 50 per cent less. Her temperature rose to 100 F. by mouth. The lesions on her scalp and on the intergluteal fold looked much better with healthy granulating tissue appearing in all areas. There was a severe local reaction on the arm from the injection. On September 6 there was continued improvement. The scalp was assuming a more healthy color. The "itching was very slight and only occasional." Prior to the injection there was a great deal of itching, so that she had to scratch very often. On September 11 the scalp looked much better. The area looked more like a superficial erosion. The base was firm and apparently healthy. Another injection of 0.5 cc. of diphtheria toxoid was given. On September 13 the area of erosion was diminishing. There was only occasional itching. The patient received three more injections of 0.5 cc. each on September 24 and 30 and on October 8, making a total of 3 cc. On October 8 the scalp was improving. The skin was more clearly approaching the normal color. The itching was only slight. There was some crusting with some denuded areas exposing the reddened surface. The scalp had lost its previous mushy appearance and grayish color. The lesion on the back had healed except for the lack of superficial epithelium.

CASE 4.—*Mycosis fungoides.*

E. L., a white woman aged 50, was presented before the New York Academy of Medicine, Section of Dermatology and Syphilis, on March 7, 1939 (ARCH. DERMAT. & SYPH. **40**:816 [Nov.] 1939); before the New York Dermatological Society on Oct. 24, 1939 and again on Oct. 22, 1940 (ibid. **43**:1045 [June] 1941). From her last presentation until Aug. 12, 1941 she had several courses of unfiltered and filtered roentgen rays (with 1 to 3 mm. of aluminum filter). She was also taking solution of potassium arsenite U. S. P. in gradually increasing doses but was obliged to discontinue this therapy when the dose reached 16 drops. The patient responded to filtered roentgen rays for a time, whereas the unfiltered radiation failed to have any effect. However, the response was only short lived, as the lesions recurred again a few weeks after the termination of the roentgen ray course.

The patient was examined on Aug. 15, 1941 and showed similar generalized lesions in the same locations as at the time of her last presentation. There was an ulcerated lesion about 3 inches (7.5 cm.) in diameter in the left temporal region and another on the left flank. The eyelids were edematous, so that the patient was able to open them only partly and with difficulty. There were numerous lesions varying from 6 to 8 inches (15 to 20 cm.) on the trunk and extremities which were well defined, purplish red and infiltrated. Some were scaly. She complained of stinging and continuous pricking sensations and of severe pruritus.

On August 15 1 cc. of diphtheria toxoid was injected in the left arm subcutaneously. The next day the itching was much less pronounced. There was a large swelling and infiltration of the arm with fever (temperature of 101 to 103 F.) and chilliness. The following day the itching was only slight and pale areas appeared in the patches, which were more scaly and less infiltrated. On August 20 the patient stated that she was fatigued and restless but that the continuous itching and stinging of the skin had almost entirely left her except for moderate itching on the face and scalp. The lesions were noticeably dryer, paler and more scaly with numerous pale areas. On August 22 there was continued improvement in all the lesions. The ulcerated patch in the left temporal region was drying up and rapidly undergoing involution. There was considerable improvement in the edema of the eyelids. Since the toxoid injection she can keep her eyes open entirely and they feel much better. On September 6 and 24

and October 2 injections of 0.5 cc. of diphtheria toxoid were given, making a total of 3 cc. On October 9 the patient appeared better and felt stronger. Most of the lesions on the body had been regressing. She complained of some itching, extreme dryness and scaliness of the lesions on the face only.

NOTE.—Laboratory tests have been done in all of these cases. They have been purposely omitted to avoid lengthy reports.

DISCUSSION

DR. MAURICE J. COSTELLO: I think that the beneficial effects observed in these patients were possibly due to the febrile reactions of this form of therapy. I have observed febrile reactions in treating lepra with as high a temperature as 106 F.

DR. GEORGE C. ANDREWS: I treated 1 patient with lupus erythematosus profundus with diphtheria toxoid, without any improvement. I also treated 2 patients with chronic allergic dermatitis without any lasting improvement.

DR. E. WILLIAM ABRAMOWITZ: I had a case of resistant cheilitis in which one injection of 0.25 cc. of the toxoid cleared up the condition. In another case a man had had a resistant psoriasiform type of eczema for nine or ten years. Nothing seemed to help him, so I gave him an intramuscular injection of toxoid about once every two months. The injections were painful, but this therapy seemed to control relapses of his eruption, which previously had been severe enough to send him to the hospital.

DR. HERMAN SHARLIT: I think there is a way of controlling a clinical study, particularly if one is willing to carry it through a long time in a number of cases. In a group of patients with mycosis fungoides, for instance, one ought to give a few patients the toxoid and a few plain distilled water instead of the toxoid. I think there is such a thing as psychic factor in therapy, which is important.

DR. DAVID BLOOM: I have treated about half a dozen patients with diphtheria toxoid. Among these were several with lupus erythematosus. I have seen no effect whatsoever from this treatment.

DR. FRED WISE: Diphtheria toxoid has been employed in other clinics for several years as experimental therapy for various rebellious cutaneous diseases. Although favorable responses to such therapy have occurred only in isolated instances, notably in leprosy, I feel that further investigations are desirable in order to evaluate this toxoid in obstinate eruptions.

CHICAGO DERMATOLOGICAL SOCIETY

LEONARD F. WEBER, M.D., *President*

MICHAEL H. EBERT, M.D., *Secretary*

Oct. 15, 1941

Acquired Multiple Pigmented Nevi. Presented by DR. FRANCIS E. SENEAR and DR. THEODORE CORNBLEET.

B. C., a white woman aged 24, presents multiple grouped dark brown pinhead-sized to slightly larger macules on the torso, extending from the buttocks to the breasts. For the past year these macules have appeared in increasing numbers, and none have disappeared, so far as the patient knows.

Histologic examination of a biopsy specimen from a lesion on the buttock showed a considerable amount of melanin pigment, the pigment granules being densely packed in the basal layer of the epidermis, in the follicle and in the cells around the follicle.

DISCUSSION

DR. S. W. BECKER: The patient's flat brown macules under the microscope show localized collections of so-called nevus cells which are still, at least in this one section, all attached to the epithelium. This is the same condition that obtained in the patient whose case was reported by Dr. Zeisler and me (Generalized Lentigo, ARCH. DERMAT. & SYPH. **33**:109 [Jan.] 1936). It is identified as a benign process because there is no extension of the cells through the epithelium to the surface. In the so-called lentigo maligna, which may appear identical but not in such great numbers, these cells are seen through the stratum corneum. In the case of acquired nevi presented by Dr. Ebert some years ago, not all the cells were attached to the epithelium; many had dropped into the stratum corneum, and the patient had what was called *"Abtropfung"* by Unna. I do not believe that this particular type of nevus ever becomes malignant. The smooth brown nevus is a dangerous type, showing an excessive number of melanotic cells uniformly scattered along the epithelium. This condition may be considered a benign hyperplasia of the clear cells.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I agree with Dr. Becker that this type of nevous rarely shows malignant change. Any nevoid condition, however, that is subject to repeated trauma or irritation may eventually become malignant.

Sporotrichosis. Presented by DR. DAVID V. OMENS, DR. A. B. FALK (by invitation) and DR. M. OTSUKA (by invitation).

Mrs. A. S., a Polish woman aged 39, presents an eruption on the flexor surface of the right forearm, which is composed of variously sized nodules in all stages of evolution distributed along the course of the lymphatic vessels. The eruption started three months ago as a papule on the wrist following a slight injury sustained while the patient was employed in a paper factory. This developed into a pustule, which ruptured, discharged its contents and healed. About one month after the appearance of the initial lesion numerous similar ones developed along the course of the lymphatic vessels. The patient states that she has not handled rabbits, plants or weeds of any kind.

Physical examination showed no abnormalities. The reaction to a Mantoux test with a 1:10,000 dilution was strongly positive. The Wassermann reaction of the blood was negative. Agglutination tests for tularemia gave negative results. Blood counts were normal. Cultures of material from the unruptured lesion were positive for Sporotrichum.

DISCUSSION

DR. H. R. FOERSTER, Milwaukee: The presenters are to be complimented on the thoroughness of this study as regards the cultures and microscopic specimens. An interesting point in this case is the absence of any suggestive lead as to the origin of the infection. In most cases the condition is apparently the sequel of minor injury at a time of contact with some form of vegetation likely to harbor the fungus. A group of cases of sporotrichosis was recently reported in Indiana, where the disease is rarely encountered; all the patients were florists and all had had preceding injuries (Gastineau, F. M.; Spolyar, L. W., and Haynes, E.: Sporotrichosis, *J. A. M. A.* **117**:1074 [Sept. 27] 1941).

DR. M. H. EBERT: This patient was observed at the Cook County Hospital for a considerable period. Diagnoses considered were a tuberculous lymphangitis, a tuberculous chancre and an early form of sporotrichosis of an unusual type because the lesions, except one, never softened. They seemed to be absorbed spontaneously. From our limited experience with sporotrichosis that is unusual.

MISS CARRIE I. WOOLSEY (by invitation): The causative agent of sporotrichosis was first isolated in this country by Schenck, in 1898, and in the same year De Beurmann reported it in France. Since then reports indicate that it has been found in various countries and in scattered parts of the United States. However, the great majority of the cases have been reported from the Mississippi River

valley, from Pennsylvania and from France. Hektoen and Perkins reported a case in 1900, and since then Sporotrichum schenckii has been isolated in more than 150 cases in this country by various workers.

Attempts to differentiate the European form from that found in this country have failed because of the variations occurring within one strain as well as the variable characteristics among strains. For example: The filaments present true branching with spores or conidia attached latterly in one culture and perhaps terminally in the next subculture. A black pigment may be formed by some strains on one medium but not on others. The intensity of the color also varies. It was thought at one time that the use of sugars differentiated the two forms by the formation of acid in lactose or sucrose. Davis and Moore, as well as Meyer, reported a variability in this reaction early in their work with Sporotrichum.

Meyer has reported much of the work done in Pennsylvania, while Ruediger, in 1912, and later Foerster, in 1924, observed that 60 per cent of the reported cases occurred in the Mississippi River valley. Of a group of 18 patients Foerster found that 14 had been infected by the barberry bush. In numerous cases the condition has occurred in farmers and florists, and hay, splinters of wood, thorns or the sharp edges of leaves have been involved. Bites of animals have been reported as causative agents in some cases.

Mycelial threads and spores are not found in the pus from the lesions, but in a Gram-stained smear cigar-shaped bacilli may be found in the cytoplasm of the polymorphonuclear leukocytes. If a male rat is inoculated with this material, the testicle becomes swollen and inflamed, and the pus from this lesion is rich in the cigar-shaped gram-positive bacilli. Agglutination tests using the spores as antigen and cutaneous tests have been tried as methods for recognizing sporotrichum infection but have not proved specific or satisfactory in the opinion of some investigators.

This fungus grows readily on Sabouraud's medium, Herrold's egg yolk agar medium and dextrose broth; after isolation, it grows easily on blood agar. To ascertain the position of the spores, one must make a broth culture mount in a hollow ground slide. The cover slip is sealed in place, and the culture may be watched for days.

Seborrheic Eczema Treated with Forty per Cent Sulfur Paste. Presented by DR. HERBERT RATTNER and DR. THEODORE CORNBLEET.

J. P., a woman aged 29, was well until seven months ago, when, after a cesarean section, there was a gradual loss of hair from the scalp. Three months ago scaling patches appeared on the scalp and ears, accompanied by a moist eruption in the axillas, under the breasts and in the groins. The application of salves aggravated the condition until finally, four weeks ago, she was admitted to the hospital with acute infected dermatitis of the areas mentioned. Therapy with dilute potassium permanganate packs, urea, boric acid and aluminum subacetate gave but little benefit. The application of a 40 per cent sulfur paste, however, effected slow but continuous improvement.

Laboratory examinations, including serologic tests, chemical determinations on the blood, blood cell counts and urinalysis, gave normal results.

DISCUSSION

DR. MAURICE OPPENHEIM (by invitation): When I had the good fortune to come to the United States, I spoke in New York about the treatment of pityriasis rosea with 25 per cent sulfur in paste of zinc oxide. The dermatologists were surprised about using such a strong sulfur ointment, being of the opinion that it would cause irritation. But it did not. In Vienna the use of highly concentrated sulfur pastes and ointments was customary. The reason sulfur sometimes causes irritation may be the fact that samples of sulfur sublimate and sulfur precipitates have an odor of hydrogen sulfide and also a taste. The Pharmacopeia of the United States prescribes that medical sulfur should have no odor and no taste;

therefore, I believe that the irritations caused by sulfur ointments are caused by the content of hydrogen sulfide and other impurities of sulfur.

DR. JAMES H. MITCHELL: Why was 40 per cent sulfur decided on?

DR. HERBERT RATTNER: We simply followed the leader. Abramovitz first used that concentration of sulfur in petrolatum. The case was presented because there is considerable difference of opinion as to the efficacy of the preparation. We have used a great deal of it at Cook County Hospital, and we have used it rather indiscriminately, often with excellent results but not always. We have not yet been able to define clearcut indications for its use, nor are we convinced that it is better to use than paste of zinc oxide N. F.

A Case for Diagnosis. Presented by DR. THEODORE CORNBLEET and DR. HENRY C. SCHORR (by invitation).

Mrs. E. D., a Negress aged 45, presents a spiny lichenoid eruption at the midline of the lumbar and sacral regions. The lesions are follicular and for the most part discrete and dry and consist of scaling pinhead-sized papules pierced by horny spines. The distribution is perfectly symmetric. It has been present for three months and is spreading. There are no subjective symptoms.

On the hard and soft palate tiny red puncta and telangiectases are present. The tongue is heavily coated. A few lichenoid lesions are present on the abdomen. Attached to the left labium minus is a lobulated mass on which there is a small ulcer. This mass has been present for ten years.

During the past year the patient has not had enough means to obtain the quality of food she formerly had.

Histologic examination showed a thin nonnucleated scale, acanthosis and lengthening of the rete pegs, edema in the upper part of the corium, vascular dilatation and a loose lymphocytic infiltrate, which lay chiefly in the upper part of the corium but also extended deeply about the blood vessels and sweat glands.

DISCUSSION

DR. JAMES H. MITCHELL: I want to ask Dr. Ebert if he remembers a patient he sent to me to be photographed; the patient had lesions down the middle of the back. That was ten years ago, but I still have the picture. I did not know what that condition was, and I do not know what the condition in this case is.

Arsenical Therapy for Chronic Ulcer. Presented by DR. MICHAEL H. EBERT.

W. L., a Negro boy aged 13, was presented for diagnosis before this society in March 1941 (ARCH. DERMAT. & SYPH. **44**:960 [Nov.] 1941). At that time an ulcer the size of a quarter was present on the perineum; it had persisted for one year. All laboratory studies, including sickle cell determinations, guinea pig inoculations, serologic tests, biopsy and culture, gave negative results.

Therapy, including repeated blood transfusions, application of mild protein silver locally, application of sulfanilamide and its derivatives locally and internally and cod liver oil dressings, was of little value in stopping the progress of the ulcer.

The patient is now shown with complete healing of the ulcer following five weekly intravenous injections of mapharsen (0.03 Gm.) and local application of cod liver oil ointment.

DISCUSSION

DR. HERBERT RATTNER: When the patient was last presented, the ulcer was large, deep and painful. The boy was in a pitiable state, for the ulcer had failed to respond to treatment despite all efforts. The result obtained from the use of mapharsen is simply remarkable.

DR. JAMES H. MITCHELL: Do you think that neoarsphenamine would have done as well?

DR. M. H. EBERT: Probably neoarsphenamine would have done as well, but a great deal of mapharsen is used in the ward, and it was given in this case in

desperation. I have never seen a more miraculous recovery. The boy was on the verge of death; he was practically kept alive by daily transfusions.

Parapsoriasis en Plaques. Presented by DR. FREDERICK R. SCHMIDT.

E. B., a white man aged 23, first noticed an eruption on his body in September 1937. It spread over his body through the winter, disappearing entirely in May of the following year. This sequence of events has been repeated each year since 1937. The patient perspires freely and does not complain of itching.

Scattered over the trunk and extremities are various-sized, sharply demarcated, round to oval patches, presenting different shades of red, yellow-brown and fawn. The scales are small, few and adherent.

Histologic examination revealed a slight degree of intercellular and intracellular edema as well as of hyperkeratosis and parakeratosis. The papillary layer showed a moderate degree of rather sharply demarcated cellular infiltration, the cells being chiefly lymphocytes, mononuclear leukocytes and a few polymorphonuclear leukocytes. Microscopic examination of the scales for fungi repeatedly gave negative results.

DISCUSSION

DR. S. ROTHMAN (by invitation): The differential diagnosis of purpura annularis telangiectodes (Majocchi's disease) should be considered. There is no scaling. Each lesion consists of flat oval macules with a yellow center and a red ring around it. This redness does not disappear on pressure and probably represents hemorrhage. The number of red blood corpuscles would be of interest, because in many cases purpura annularis telangiectodes is associated with polycythemia. Spontaneous disappearance of the lesions is most unusual in parapsoriasis en plaques.

DR. HARRY FOERSTER, Milwaukee: This case impressed me as one of toxic erythema in which there had been sufficient local irritation to produce a hemorrhagic type of lesion rather than the common variety of erythematous macules and annular lesions seen in eruptions of the erythema multiforme group. The lesions are said to have undergone involution rapidly and have recurred seasonally, a point against a diagnosis of parapsoriasis. There is no history of medication and none of toxemia, but the patient said that in one recent recurrence he had severe diarrhea at the time of onset of the eruption.

DR. FREDERICK R. SCHMIDT: Scaling does not have to be present in lesions of parapsoriasis. It may be moderate or slight. There are seasonal recurrences in certain cases of parapsoriasis en plaques. I thought the microscopic structure in this case was compatible with parapsoriasis en plaques. A form of hemorrhagic parapsoriasis was described in the French literature ten or twelve years ago which I thought fittted the condition in this case. The seasonal incidence was the reason for my presenting this case.

Pemphigus Erythematodes (Senear-Usher). Presented by DR. S. J. ZAKON (by invitation).

S. P., a Jew aged 69, born in Poland, was admitted to the Mount Sinai Hospital on July 6, 1941 because of large blisters on his scalp and face which first appeared about three months previously. In spite of therapy the eruption spread to the chest, back and abdomen.

Examination disclosed a well nourished man who presented lesions on the scalp, face, chest and back consisting of flaccid bullae on a noninflammatory base and greasy crusts. The area over the sternum, the nose and forehead were erythematous and covered with soft scales that were easy to remove. The itching and burning were intense. The mucous membranes of the mouth were not involved. The Nikolsky sign was present.

There was 15.6 Gm. of hemoglobin per hundred cubic centimeters. A blood count showed 5,500,000 erythrocytes and 9,900 leukocytes, with a differential dis-

tribution of 65 per cent segmented forms, 28 per cent small lymphocytes, 4 per cent monocytes and 3 per cent stab cells. The Wassermann reaction was negative. The urinalysis showed a trace of albumin and hyaline casts.

After venesection and removal of 500 cc. of blood, the patient was given a transfusion of 500 cc. of blood. Although the donor's blood was of the same type and there was no cross agglutination, the patient had severe chills and high fever, with a temperature of 104 F. The fever lasted for twenty-four hours and, incidentally, had a beneficial effect on the involution of the lesions. Blood taken from another donor and given by the same Baxter method did not produce any febrile reaction. In all, five blood transfusions were given.

The patient left the hospital on July 19, greatly improved. Since that time the treatment has consisted of administration of 0.25 Gm. tablets of acetarsone, ultraviolet irradiation and autohemotherapy twice a week, with potassium permanganate baths and application of boric acid ointment locally. He is back at work as a newspaper vendor.

DR. FRANCIS E. SENEAR: I agree with the diagnosis of pemphigus erythematosus and feel that the condition in this case is a typical example of the disease. In support of the opinion that an eruption of this kind should be classed as a type of pemphigus, I should like to state again that the last patient who came under my observation at the Research and Educational Hospital, University of Illinois, first showed a typical benign type of involvement. Within a short time a picture developed which was equally typical of pemphigus vulgaris, and then death, ensued within a few weeks. I am familiar with the histories of 5 or 6 other cases in which a comparable sequence occurred.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I believe that the histopathologic picture of pemphigus erythematodes is distinct from that of lupus erythematosus and shows much more inflammatory reaction than that of pemphigus vulgaris. Wise and others have emphasized that in many cases a condition described as the Senear-Usher syndrome has been simply a bullous lupus erythematosus. Dr. Ormsby, Dr. Wise and I felt that this was true of a case reported by Taussig. Numerous cases presented before this society, however, and others presented by Dr. Wile and Dr. Belote have fulfilled all the requirements of the Senear-Usher syndrome.

DR. MAURICE OPPENHEIM (by invitation): This condition is no doubt pemphigus, because of the duration. The disease started behind the left ear as a bullous eruption and then after a few months became generalized. This brings up again the question of a primary lesion of pemphigus. Perhaps some eruptions classified as the Senear-Usher syndrome are primary lesions of pemphigus. Another point is that Dr. Zakon administered acetarsone, which I recommended first for pemphigus, and he observed improvement. The treatment must be continued, according to my schedule, sometimes up to 200 and eventually 400 tablets. Then one can obtain excellent results.

Arsenical Reaction Encountered in the Five Day Treatment for Syphilis (Nephritis, Hepatitis and Pericarditis). Presented by DR. HERBERT RATTNER and DR. ALFRED B. FALK (by invitation).

J. W., a Negro aged 23, entered the Cook County Hospital on Aug. 7, 1941 with a penile chancre of four weeks' duration and a papular syphiloderm of the body. Dark field examination showed organisms, and serologic tests elicited positive reactions. Aside from the syphilis the patient was in good health, and other than typhoid fever in 1933 there were no previous illnesses.

Laboratory studies, including chemical determination on the blood, urinalysis, blood counts, determination of the icteric index and roentgenographic examination of the chest, gave normal results. Treatment by the intensive five day method was then instituted.

After but one day of treatment, during which the patient received 0.24 Gm. of mapharsen in 2,000 cc. of 5 per cent dextrose solution intravenously, the following

conditions developed: acute glomerulonephritis, anuria for eighty hours, hepatitis, ileus for forty-eight hours, pericarditis of two weeks' duration and uremia with uremic frost. At the peak of the reaction the nonprotein nitrogen content of the blood rose to 170 mg. per hundred cubic centimeters and the creatinine content to 16.8 mg. Despite the overwhelming reaction, the patient made an uneventful recovery from all symptoms except for inability to concentrate urine above 1.010. A serologic test of the blood ten weeks after the one day of treatment gave a negative reaction.

DISCUSSION

DR. EDWARD A. OLIVER: I should like to ask Dr. Rattner to tell a little more about the reactions they have had: whether this was one of the worst; if they had others, and if so what they were.

DR. HERBERT RATTNER: This is the first reaction of its kind reported in 1,500 to 1,800 cases throughout the country in which this treatment was given. In fact, one of the surprisingly satisfactory features about the five day treatment of syphilis has been the lack of injury to the kidneys and other parenchymatous organs. There have been a number of cases of encephalopathy reported, but other than this the reactions have been minor ones. I have observed 2 cases of encephalopathy, in both of which there was recovery without apparent sequelae and in both of which there was reversal of serologic reactions. The most disturbing of the minor reactions are pain in the arm, nausea and vomiting and fever, which occur in about half the cases. In our 265 cases we have had to interrupt treatment but 4 times because the temperature reached 101.4 F., when arbitrarily treatment is stopped. In every case we were able to resume treatment on the next day.

The occurrence of encephalopathy is, of course, the serious drawback to general acceptance of the method. There has been an incidence, I think, of about 1 fatal cerebral accident for every 200 or 250 patients treated. Fortunately, there have been no fatalities at the Cook County Hospital. It is not known whether this incidence is high or low as compared with standard treatment, and, in all fairness to the method, its fatality rate should be compared with the incidence of death from all reactions encountered in standard treatment. Nor should statistical comparison be made with the number of injections in standard treatment. An interesting feature in this regard occurred at the meeting of the American Medical Association in Cleveland, where the Public Health Service had a booth in which the five day treatment was illustrated. On one day some 75 visiting physicians told the attendant of about 125 deaths from standard treatment encountered in their practices, and these were deaths that were never reported in the literature and, indeed, not recorded as treatment deaths. It therefore seems impossible to make a reliable statistical comparison between the two methods as regards fatal accidents.

DR. MINNIE O. PERLSTEIN: I should like to ask Dr. Rattner about the use of the five day treatment for children.

DR. HERBERT RATTNER: I have not kept myself well informed, but in the children's department the results in the treatment of congenital syphilis by the intensive method are apparently similar to those obtained generally in older syphilitic patients. Incidentally, in our series we have treated 10 pregnant women with secondary syphilis. Five of them have given birth to healthy babies, and the others are awaiting delivery. The oldest baby is about 11 months of age; the pregnancies have ranged from 2 months to almost term at the time of treatment. Our results in general have encouraged us to continue with the treatment, albeit we look on it as a clinical experiment.

DR. OTTO H. FOERSTER, Milwaukee: It should be emphasized that the five day treatment is still in an experimental stage, is an institutional procedure accompanied by definite hazards and should be reserved exclusively for syphilis in the early stages. As carried on with the cooperation of the United States Public Health Service it is an entirely experimental project. I regret to report a death following this treatment. The patient was a woman, later found to have been an alcoholic addict, who had two genital chancres and who was given this treatment

only after she had passed a thorough and detailed physical examination. On the day after the treatment was completed, a universal blotchy erythema rapidly developed, and she soon became unconscious, had several convulsions and died. A complete autopsy done by members of the department of pathology of the University of Wisconsin showed no single specific mechanical cause for death, and nothing was observed in the brain which could be interpreted as hemorrhagic encephalitis.

Dr. Norman Tobias (by invitation), St. Louis: In the St. Louis series of 125 patients treated with the five day method, there has been 1 death, that of a 17 year old Negress, and this was due to acute hemolytic anemia that appeared on the fifth day of treatment. The condition began with general aches and pains, faintly bloody sputum and blood-streaked stools. The next day jaundice, a rapidly falling red blood cell count and hematuria were present; she had a convulsion, became comatose with absence of reflexes and died. Hematologic studies verified the diagnosis of acute hemolytic anemia. The collapse was so sudden that transfusions were ineffectual. Whether there was a disturbance of the reticuloendothelial system, the spleen or the red blood cells themselves is a matter that is difficult to explain. Postmortem examination, including that of the brain, revealed no information of value.

Dr. Herbert Rattner: I know of 2 other cases in which the condition was fatal and in which the clinical diagnosis was hemorrhagic encephalitis. On autopsy, however, the pathologists could not confirm this diagnosis either grossly or microscopically. In all, the midwestern cooperative group that is conducting the study has encountered 5 fatalities in some 1,000 cases. These include the cases mentioned by Drs. Foerster and Tobias.

A Case for Diagnosis. Presented by Dr. A. R. Koransky (by invitation) and Dr. Edward A. Oliver.

A white man aged 50, a molder by trade, was seen in the dermatologic clinic of Northwestern University on July 14, 1941 because of an eruption on the back which had been noticeable for the past two years. He stated that the eruption had not caused much discomfort except for occasional itching and moderate pain at times. The itching was especially noticeable when he removed his clothes. The eruption did not interfere with his work.

Examination revealed a nodular eruption on the back. One node measured 7 cm. in diameter and was elevated, indurated and fixed in the skin; it was oval and purple-red, and the surface was rough. This node was located near the lower vertebral border of the right scapula. A node of similar description, measuring 3 by 5 cm., was located in the midline and almost adjoined the one described. An oval area 8 cm. in diameter, blotchy red, slightly indurated and not raised, was located over the left scapula. A group of nodes was found in the lumbosacral region, the largest of which measured up to 2 cm. The nodes in this group were elevated, indurated and fixed in the skin and were pinkish red. Enlargement of the preauricular, cervical, axillary and inguinal glands was present.

Other findings were a lipoma of the right forearm and varicosities of the lower extremities.

Examination of the blood on July 12 revealed 5,200,000 erythrocytes, 17 Gm. of hemoglobin and 5,650 leukocytes, with a differential count of polymorphonuclear neutrophils 3 per cent, polymorphonuclear filaments 66 per cent, basophils 1 per cent, lymphocytes 28 per cent and monocytes 2 per cent. On July 27 examination of the blood revealed 4,910,000 erythrocytes, 15 Gm. of hemoglobin and 4,800 leukocytes, with a differential distribution of polymorphonuclear neutrophils 5 per cent, polymorphonuclear filaments 73 per cent and lymphocytes 22 per cent.

Urinalysis showed a 2 plus reaction for albumin. The Kahn reaction was negative. A roentgenogram of the chest showed a rather diffuse increase in the density throughout the pulmonary field.

Specimens for histologic examination were taken from two sites, one from an older lesion and another from a younger lesion. Sections from the older lesion

revealed a moderately acanthotic and edematous epidermis. The papillary portion of the corium had only a sparse infiltrate. Beginning with the upper third of the corium, the infiltrate became progressively denser and appeared in chains or columns of cells of a polymorphous character and enmeshed in and between the connective tissue fibers or mantles about the blood vessels, sweat glands and pilosebaceous structures. In the lower part of the corium and subcutaneous tissue the infiltrate was both nodular and diffuse. The cells making up the infiltrate were small lymphocytes, large and small fibroblasts, polymorphonuclear leukocytes, plasma cells, lymphoblasts, epithelioid cells and eosinophils. A granular degeneration of the cell bodies was evident in some areas. The blood vessels were numerous, particularly in the infiltrated areas, and some appeared to be newly formed. The collagen fibers of the reticulum were swollen and fragmented; the elastic fibers were in parts broken and diminished. The tissue from the younger lesion was generally similar to the tissue just described. The polymorphous character of the infiltrate, however, was much more pronounced.

During the past three months the patient has received roentgen ray treatment, totaling 1,260 r in fractional doses, and the tumors have undergone rapid involution.

DISCUSSION

DR. CLARK W. FINNERUD: I saw the sections. They were of little help. There was a history of response to roentgen therapy. The condition impressed me as being a lymphoblastoma of some sort, possibly mycosis fungoides, but I could not classify it definitely.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Some of the sections were strongly suggestive of mycosis fungoides. Sections of the deeper lesions were more suggestive of a chronic nonsuppurative panniculitis. I believe this condition, however, fits in better with a deep-seated type of lymphoblastoma, which is different from the ordinary tumor type stage of mycosis fungoides.

DR. EDWARD A. OLIVER: I am inclined to agree with Dr. Montgomery's suggestion. When I first saw the patient, I made a diagnosis of spindle cell sarcoma. Several of the histologic reports suggested mycosis fungoides. If the condition in this case is mycosis fungoides, it must be of the d'emblée type. I do not believe it is, however, because in most cases of this type there is a tumor of a mushroom type. The man is improving so well with small doses of radiotherapy that I withdraw my diagnosis of spindle cell sarcoma.

Accidental Tattoo. Presented by DR. LEONARD F. WEBER.

H. E., a white man aged 26, was in an explosion on Oct. 7, 1941. The foreign particles that were embedded in the skin of his face consisted of cinders, dust and chilled shot. Many of the larger particles were removed on the day of the accident, and since then smaller particules have been removed daily. There were no foreign bodies in the eyes because of the protection afforded by goggles.

DISCUSSION

DR. LEONARD F. WEBER: In the treatment of accidental tattoo I have not used a local or general anesthetic. It has been my practice if an anesthetic is needed for the removal of powder stains and similar stains to give whisky. As a rule that quiets the patient enough to permit uninterrupted work. I think dermatologists from time to time see patients with this condition six months to a year after the accident; the surgeon usually sends them to the dermatologist. A few can be helped and others not. All depends on the depth of the cinders or foreign bodies and the time that has lapsed since the accident. If the pigmented masses are deep in the corium a good many cannot be removed. In a few cases, although the foreign bodies are deep, they can be removed and are followed by scars. Good results can be secured by early removal. This patient had dust, ordinary cinders and small chilled shot embedded in the skin of the face. The treatment was largely mechanical and was successful because it was started within a few

hours after the accident, before the particles of pigment had become so disintegrated that their mechanical removal would be impossible. The individual masses were patiently picked out, for which an iris needle and a small sharp-pointed knife were convenient. The method required great patience both on the part of the man and on my part. The larger masses and bodies were removed first, without subsequent infection. Later the smaller ones were removed. A total of thirty-five hours of work divided over a period of three weeks gave the result.

DR. EDWARD A. OLIVER: Dr. Weber has modestly presented several cases of this kind. In this case I think that he has achieved a most excellent result, and I hope that he will feel encouraged to show us more of his results.

Scleroderma. Presented by DR. HERBERT RATTNER and DR. THEODORE CORNBLEET.

M. G., a white woman aged 48, was well until 1939, when she noticed tingling sensations and blanching of her fingers on exposure to cold. After a few months she became aware of the difficulty in making fine movements with her fingers and her feet began to feel stiff. Gradually a feeling of stiffness appeared in the skin of the chest. The past history is essentially normal.

The fingers are now somewhat cyanotic, and on the hands and feet the skin is firmly adherent to the underlying structures. There is a binding down of the skin of the trunk but to a lesser degree.

Examination of the blood showed hemoglobin 64 per cent, erythrocytes 3,450,000 and leukocytes 10,700, with a differential count of polymorphonuclear neutrophils 80 per cent, eosinophils 3 per cent, lymphocytes 10 per cent and monocytes 7 per cent. Chemical examination of the blood gave the following results: nonprotein nitrogen, 24 mg. per hundred cubic centimeters; creatinine, 1.2 mg.; calcium, 9.9 mg.; phosphorus, 4.1 mg., and phosphatase, 7.52 mg. The basal metabolic rate was —2 per cent. The urine and a roentgenogram of the chest were normal.

The histologic picture was that of scleroderma.

DISCUSSION

DR. RUBEN NOMLAND, Iowa City: I should like to call attention to the fact that while this woman had a sclerodermatous involvement of the hands she did not have acrosclerosis. She had the ordinary type of diffuse scleroderma.

DR. NORMAN TOBIAS (by invitation), St. Louis: I should like to ask if any one has had any success with ammonium chloride. I had a patient about 12 years of age who reacted well to the drug. The beneficial effect of the drug in this case was difficult to evaluate, as there was no elevation of the calcium level of the blood or clinical calcinosis. Spontaneous recovery, however, has been reported in scleroderma.

DR. EDWARD A. OLIVER: I have tried ammonium chloride in 2 or 3 cases of localized scleroderma with good results. I should like to ask the presenters if they have tried pancreatic extract in this case.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I agree with Dr. Nomland that this condition is diffuse scleroderma with sclerodactylia and is not acrosclerosis. I have not had any experience at the clinic in the use of histaminase and ammonium chloride for these conditions. Pancreatic extracts have apparently been without beneficial results.

DR. HERBERT RATTNER: There have been reports of excellent results from the use of dihydrotachysterol. We have been using histamine administered by iontophoresis, but in 2 of our cases there was a fatal termination.

Pemphigus Vulgaris Treated with Acetarsone. Presented by DR. MICHAEL H. EBERT.

F. B., a Negress aged 41, was well until eight months ago, when she noticed a blister in her mouth which did not heal. Within a month numerous blisters appeared on the sides of the neck and then became generalized. On examination

numerous bullae were seen arising out of seemingly normal skin with no erythema or tendency toward grouping.

A diagnosis of pemphigus vulgaris was made, and therapy with acetarsone was started in June 1941. By September all the lesions had healed and the patient had gained approximately 20 pounds (9 Kg.) in weight. She was allowed to leave the hospital but returned in two weeks with a new outbreak of bullae following an intercurrent infection in the upper part of the respiratory tract. During the period at home she had neglected to continue taking the acetarsone. She has been returned to the ward, and this therapy has been continued.

The essential feature of the past history is that two years ago she noticed a fulness in her neck associated with weakness and loss of weight. She was told that she had "thyroid disease" and was given drops to take. She has taken none of this medicine for the past year.

The results of laboratory studies, including serologic tests, urinalysis (including iodine determination), chemical examination of the blood and blood counts, were all within normal limits.

DISCUSSION

DR. M. H. EBERT: There was no doubt that this was a case of pemphigus. The improvement with acetarsone is remarkable. While not entirely well, the patient shows as much improvement as I have seen. How long she can tolerate the arsenic is a question.

A Case for Diagnosis (Lichen Planus with Atrophy?). Presented by DR. MICHAEL H. EBERT and DR. ALFRED B. FALK (by invitation).

W. L., a Negress aged 55, first noticed itching between her shoulders one year ago and an eruption in this area that could be palpated. About six months ago she noticed small white patches appearing on her chest associated with a tingling sensation of the skin.

On examination there are split pea-sized whitish atrophic lesions on the chest, abdomen and back. The lesions are discrete, many having a central pigmented zone. In the left infraclavicular region there are a few angular pigmented papules. On the flexor surfaces of the wrists is a residual pigmentation.

The past history and general medical examination revealed no abnormalities.

The results of laboratory studies were within normal limits except that analysis of the gastric contents after an Ewald meal showed a total gastric acidity of 4 and a value for free acid of 0.

DISCUSSION

DR. STEPHAN EPSTEIN, Marshfield, Wis.: I am impressed by the relative frequency with which lichen planus occurs in persons who either are extremely nervous or run-down or have had a recent nervous upset. In this case the disease probably occurred after the death of the patient's husband. This brings up the question of treatment with vitamin B complex, on which I reported in 1939 (ARCH. DERMAT. & SYPH. **41**:620-621 [March] 1940). Burgess (*Canad. M. A. J.* **44**:120, 1941) felt that the war strain had increased the incidence of lichen planus. He reported a series of 15 patients who had been benefited by vitamin B complex. It is not known which factor of the complex may be responsible. Tzanck, Sichi and Tardieu (*Bull. Soc. franç. de dermat. et syph.* **46**:862-864, 1939) reported 3 cases of lichen planus with great improvement from nicotinic acid amide.

In 1 of my patients the condition cleared almost completely after treatment with vitamin B_1, but subsequently she had a recurrence. Since then, I have treated a few more patients successfully with vitamin B complex.

DR. RUBEN NOMLAND, Iowa City: I believe that Dr. Ebert's patient has ordinary lichen planus with atrophic lesions. The condition is not lichen sclerosus et atrophicus. I do not know anything about the treatment of lichen planus with vitamin B complex except that I had one failure.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I disagree with the diagnosis as given. I think this condition is a classic picture of lichen sclerosus et atrophicus both clinically and histologically. This condition has nothing to do with lichen planus or with the patient's being nervous. There is a little more scaling to the lesions than one usually sees in the white race. This is the first time I have seen lichen sclerosus in a Negro. The distribution of the lesions about the breasts and on the back of the neck is classic. There is slight liquefaction degeneration of the basal cell layer with the typical area of edema just beneath it and the infiltrate appearing only below the area of edema. Csillag's disease is lichen sclerosus et atrophicus. Histologically, one sees that the elastic tissue is separated from the epidermis by edema with mucin-like substance that does not take stains for mucin. Lichen sclerosus will not respond to any treatment. Occasionally the lesions undergo spontaneous involvement, but that is the exception to the rule.

A Case for Diagnosis. Presented by DR. THEODORE CORNBLEET and DR. DAVID COHEN (by invitation).

A woman aged 53, who has diabetes, shows a slightly pruritic eruption on the neck and chest, which she has had for one year. The lesions consist of papules arranged in a circinate manner.

Histologic examination of the skin from the neck showed a well circumscribed zone of cellular infiltration in the subpapillary part of the corium. Within this zone there were mantles composed chiefly of lymphocytes and histiocytes about the blood vessels. Staining with sudan III showed many lipid droplets with many cells in this area. Elsewhere in the subpapillary corium the blood vessels were dilated and surrounded by a narrow zone of these cells.

DISCUSSION

DR. M. J. REUTER, Milwaukee: I thought the condition belonged in the erythema perstans group. I can never remember the various subclassifications of this group. Clinically there was nothing to suggest necrobiosis diabeticorum.

DR. HERBERT RATTNER: There have been suggestions recently to link granuloma annulare and necrobiosis lipoidica diabeticorum. I wondered if the condition in this case did not fit into that group.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I did not see any evidence histologically of granuloma annulare. The extracellular deposits of lipids suggested necrobiosis lipoidica diabeticorum, with which condition the clinical picture, however, does not correspond. This patient presents a new condition to me.

DR. RUBEN NOMLAND, Iowa City: I recently had the opportunity to observe a diabetic patient with erythematous annular lesions on the legs of relatively recent origin. I thought the condition was necrobiosis, and a histologic section looked a good deal like the section presented today. Strangely enough, in a relatively short time the diabetes was controlled and the necrobiotic lesions disappeared. I believe this is contrary to the general course of events. Usually the necrobiotic lesions do not disappear on diabetic management. It may be a new disease or similar to the necrobiosis occurring in diabetes.

DR. CLARK W. FINNERUD: I do not know what this lesion is. I had a patient a couple of years ago with a similar clinical picture. Because of the history, an atypical necrobiosis, granuloma annulare, erythema annulare centrifugum and tuberculid were considered, but in this particular instance histologic examination showed a sarcoid-like structure. The final diagnosis was sarcoid.

DR. MARCUS R. CARO: I do not believe that it is possible to make a histologic diagnosis of necrobiosis lipoidica diabeticorum here. The section stained with sudan III shows a considerable amount of lipids, but the droplets are largely intracellular. Clinically, however, it is possible for annular lesions to occur in necrobiosis lipoidica diabeticorum. About three years ago I had as a patient at the University of Illinois a man of 72 who had a single annular lesion on the back of the hand; a clinical diagnosis of granuloma annulare was made. The

histologic section showed the condition to be necrobiosis lipoidica diabeticorum, and on further examination the patient was found to have diabetes mellitus.

DR. MAURICE OPPENHEIM (by invitation): At the meeting of the American Medical Association in Cleveland, Ellis tried to bring proof that granuloma annulare and dermatitis atrophicans are identical, but, as Montgomery stated on that occasion, they are entirely different clinically and also histologically. The clinical picture of dermatitis atrophicans diabetica is sharply defined. It is found only in diabetic patients. If in a few cases diabetes was not found, then in these cases the condition was latent or there was a diabetic family history. As I have stated on various occasions, I believe that the name dermatitis atrophicans lipoides diabetica is more correct than the term necrobiosis lipoidica.

DR. HERBERT RATTNER: There is a man in the medical service at Cook County Hospital now with a large lesion, the size of a dollar, on each hand. The clinical picture strongly suggests granuloma annulare. I am told that he is the same man to whom Dr. Caro referred.

Parapsoriasis with Features of Poikiloderma Vasculare Atrophicans. Presented by DR. HERBERT RATTNER and DR. MAURICE DORNE.

M. S., a white woman aged 60, presents a slowly progressive, erythematous, dry, scaling, patchy eruption on the trunk and extremities of twenty-five years' duration. Some of the patches, particularly one on the right breast, present a diffuse network of dilated capillaries associated with atrophy and pigmentation. There are no subjective symptoms.

The basal metabolic rate was reported as —16 per cent. The chemical examination of the blood gave normal results.

Histologic examination of a section from a lesion on the abdomen showed considerable intercellular and intracellular edema of the epidermis. In one area the epidermal cells were ballooned and had the nuclei flattened to one side. There was a thin scale with areas of parakeratosis. The upper part of the corium was edematous and contained dilated lymphatics and blood vessels. About these, especially in the papillary layer, there was a dense cellular infiltrate in which lymphocytes predominated. In places these cells invaded the epidermis. A section taken from a lesion on the thigh showed identical changes to a lesser degree.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: The histologic changes are compatible with those of poikiloderma, and the clinical picture is more that of a poikiloderma than that of any form of parapsoriasis. It is questionable whether poikiloderma vasculare atrophicans is a disease entity. In the past, cases were reported of this condition in association with tuberculosis and lymphoblastomas, and at the Mayo Clinic I have observed several cases of the disease associated with the latter condition and also with subacute disseminate lupus erythematosus and with scleroderma.

DR. S. ROTHMAN (by invitation): This patient was seen in Billings Hospital, and a clinical and histologic diagnosis of poikiloderma vasculare atrophicans was made. I agree with Dr. Rattner that the condition is rather atypical, but I wonder if one is justified in classifying it as parapsoriasis.

A Case for Diagnosis (Eczematoid Dermatitis? Lymphoblastoma?). Presented by DR. CLARK W. FINNERUD.

A woman aged 40 was first seen on Feb. 24, 1941 because of a burning and slightly itching eruption which involved chiefly the lower extremities and the back; at that time it was of one year's duration, although it had been worse in the three months previous to this visit. She stated that it began as weeping and scaling patches on the forehead, scalp and ears chiefly and that as the result of the use of local preparations it entirely cleared. She had been using tincture of iodine, hydrogen peroxide and petrolatum on the lesions which were present at

the time of her first visit. She stated that her right leg, her upper extremities and the right side of the trunk had been burned with hot coffee in infancy and that ever since then any eruption or injury to the skin in these areas had healed extremely slowly. There was no history of taking phenolphthalein.

The patient presents several dozen rather sharply defined areas of erythematous scaling and crusting dermatitis of the lower extremities chiefly but with a few such lesions on the trunk. Scarring from her burns of the skin in infancy is evident, particularly on the upper extremities. The right leg is considerably swollen. There is no superficial lymphadenopathy.

The urine has at all times been normal. Serologic reactions were negative. The lowest white blood cell count recorded has been 8,300 and the highest 9,740. The average polymorphonuclear cell count has been 72 per cent and the average lymphocyte count 25 per cent, and there has never been more than 1 per cent eosinophils encountered.

Histologic sections showed considerable pyknosis and shriveling of the nuclei of the cells, spongiosis, vesicle formation, disintegrating polymorphonuclear leukocytes and other inflammatory changes compatible with eczema. These sections were examined recently by Dr. Hamilton Montgomery, who concluded from the history and from the histologic sections that this condition was a toxic process rather than a manifestation of one of the lymphoblastomas.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: There was a toxic reaction with degenerative changes in the infiltrate in the cutis simulating mycosis fungoides, but there was no clumping of the cells or immaturity of the cells of the infiltrate. The changes in the epidermis fitted in with an eczematoid dermatitis. When I saw this patient today I thought first of a fixed drug eruption, and the histologic picture would not be against such a diagnosis. This patient gives a history of having reacted to quinine in the past with gastrointestinal upset. She states that she has not taken any phenolphthalein, but I still should suspect a fixed drug eruption rather than either of the other two conditions.

DR. STEPHAN EPSTEIN (by invitation), Marshfield, Wis.: I was under the impression that the condition was a drug eruption. I have been fooled so many times in cases of drug eruption that I never accept a history that no drugs have been taken except when the disease is proved to have some other cause. I wonder if acetylsalicylic acid has been eliminated in this case.

DR. CLARK W. FINNERUD: Dr. Coomber and I have gone very thoroughly into the drug history. Bile salts were taken in 1936, and, with the exception of 1 tablet or capsule that was taken two years ago, she has taken nothing. She emphatically declares that she never takes anything except plain liquid petrolatum, an extremely occasional tablet of acetylsalicylic acid and magnesia magma. If one goes carefully into the history, and she is a cooperative person, one will certainly have to rule out drug taking as being responsible for the eruption, unless the extremely occasional aspirin that she takes is producing this picture.

A Case for Diagnosis (Poikiloderma Vasculare Atrophicans? Prefungoid Stage of Mycosis Fungoides?). Presented by DR. EVANGELINE E. STENHOUSE (by invitation) and DR. S. W. BECKER.

M. L. W., a 43 year old housewife, born in France, entered the clinic in August 1941, complaining of dry, scaling skin. Her skin had always been dry. In 1936, on her return from a beach, she noted large bullae on the legs. In the fall of that year, while standing over a hot radiator, she noted an eruption on the body which resembled scarlet fever. Scaliness was then noted on the face, neck, thighs, abdomen, chest, scalp and back in the order named. The condition was said to be worse in winter and after bathing. The skin peeled easily. There was no pruritus. Treatment by several physicians included ultraviolet irradiation, administration of tonics, vitamins and arsenic capsules, applications of salves, autohemic injections, prescription of a special diet and colloid baths.

There was a past history of amebic dysentery. A pelvic operation had been performed twenty years previously. The tonsils and adenoids had been removed. A history by systems revealed general fatigue and aching in cold weather. There had been swelling of the face and eyelids in the morning and edema of the ankles in the evening.

On physical examination, a blood pressure of 140 systolic and 95 diastolic and enlargement of the axillary and postcervical nodes were significant findings. The skin exhibited a generalized macular erythema with scaliness, areas of lichenification and telangiectases, the latter more pronounced on the breasts. There were longitudinal ridges, with splitting and thinning of the nails.

Laboratory studies showed occasional traces of a reducing substance in the urine, a normal blood count and negative Kolmer and Kahn reactions of the blood serum. The dextrose tolerance test indicated a slightly reduced tolerance. Evaluation of the patient's diet indicated a deficiency chiefly of calcium, phosphorus, thiamine and possibly other members of the vitamin B complex.

Treatment consisted of applications of bland ointments. Thorium-X in an oxycholesterol-petrolatum ointment base was applied to an area on the back and another on the left breast.

Microscopic section showed hyperkeratosis with loosening of the stratum corneum. The stratum granulosum was represented by two layers of cells containing pale-staining, loosely arranged basophilic granules. The stratum mucosum seemed to be somewhat thinned and showed no changes in the rete. The basal portion was involved in intercellular and intracellular edema with liquefaction necrosis and infiltration of the basal portion by round cells. The basal layer was indistinct throughout, there being no definite palisade arrangement. The superficial dermis contained many new-formed capillaries and small blood vessels with considerable round cell and plasma cell infiltration, predominantly perivascular. The endothelial cells were swollen. The deeper portion of the dermis appeared to be normal.

DISCUSSION

DR. S. W. BECKER: I think this is the patient to whom Dr. Foerster was referring in his discussion of another case. She states that when the weather gets bad the itching becomes unbearable. We have been able to produce some slight improvement by the application of thorium-X.

A Case for Diagnosis. Presented by DR. FRANCIS E. SENEAR.

J. K., a girl aged 9½ months, was first seen on Aug. 23, 1941 and at that time presented a remarkable picture, the chest being covered with groups and lines of vesicles to bullae with a pattern like that of severe poison ivy dermatitis. On the side of the trunk were urticarial wheals, some of them with fine vesicles. On the upper parts of the arms there were also urticarial wheals of various shapes, including lines. Dermographia was pronounced. On the heavily affected parts of the trunk and arms the skin generally was turgid and red and showed a diffuse response to rubbing. There were also numerous small bullae and vesicles on the scalp, face and sides of the neck.

According to the history, "blisters" began to develop on the palms and soles when the baby was about 10 days old. From that time on she had lesions almost continuously some place on the body. When she was 5 to 5½ months old the lesions began to appear on the head, neck, trunk and extremities, in some places as bullae and in other places as white edematous lines. She seemed to have exacerbations with fresh outbreaks of large bullae about every two weeks, these lasting four to five days and being followed by a period of relative quiescence lasting seven to nine days. She has never been completely free of lesions since the trouble began. Red lines develop wherever she scratches; these soon become white lines, and vesicular or bullous lesions develop along the course of many of them. When the skin is rubbed, the traumatized area becomes generally reddened.

The paternal great grandfather had asthma and the maternal grandfather had "a little asthma." The child was born at full term and was completely breast fed for one month. In addition she received orange juice and cod liver oil. She was given the bottle at 1 month of age and has been bottle fed up to the present, first with cow's milk and then with goat's milk.

DISCUSSION

DR. M. J. REUTER, Milwaukee: I do not know what the diagnosis is, but the case is most unusual. Vesicles occur in the scratch marks, and the child has urticarial and bullous lesions. I suppose one might be justified in making a diagnosis of dermatitis herpetiformis.

DR. C. W. LAYMON, Minneapolis: In the diagnosis I thought of dermatitis herpetiformis and epidermolysis bullosa. As Dr. Reuter mentioned, the former seems more likely, although the features of the case do not entirely fit either possibility.

DR. EDWARD A. OLIVER: I believe that in this case a diagnosis of dermatitis herpetiformis should be considered. Conditions of this kind do not run the same type of course in children as in adults. Often there is little itching; there is no definite grouping of the lesions, and bullae are invariably present.

DR. CLARK W. FINNERUD: I have never encountered a case like this. I do not see why urticaria in a tender skin, if severe enough, could not lead to a toxic eruption which at times, because of its severity, could assume a vesicular and bullous character. I think it is proper to class the condition in this case as an unusual form of toxic erythema.

DR. FRANCIS E. SENEAR: I might say that the history as read applies to the patient as I saw her originally. The urticarial element was an outstanding feature at that time. Today there is little in the way of wheals. This eruption presents exacerbations and remissions. Before the child was shown today I scratched her back with a tongue depressor, and when I saw her a little later the dermographia was so intense that vesicles had formed. One occasionally sees an urticarial type of dermatitis herpetiformis, but I am inclined to agree with Dr. Finnerud that in this case the condition is an excessive reaction in a patient with urticaria. There has been no change in the lesions at any time which would indicate papular urticaria in childhood rather than simple urticaria.

A Case for Diagnosis (Eosinophilic Leukemia?). Presented by DR. STEPHEN ROTHMAN (by invitation).

H. J., aged 45, born in Kansas, had been a clean-up man for a local automobile company for eight years. During this time he worked continuously with machine oils and kerosene. He had had no serious illness until about six months previously, when an itching pink rash appeared on the hands and ankles and soon spread to the trunk. In the middle of September 1941 his neck and forehead and later the face became red and subsequently swollen and stiff.

When the patient was first seen in the clinic, on September 22, the individual lesions of the trunk and extremities were erythematous urticarial papules with hemorrhagic or crusted tops. The face and neck were slightly edematous and displayed an eruption consisting of dark red edematous patches.

On admission to the hospital on September 26 the patient presented giant edema of the face, neck, hands and wrists and profuse cutaneous hemorrhages in bizarre figures irregularly spread all over the body and over the palate.

Urinalysis showed occasional faint traces of albumin and numerous white blood cells, apparently due to an old prostatic infection. The Wassermann and Kahn reactions of the blood serum were negative. The first blood count showed 11,500 leukocytes, with 60 per cent polymorphonuclear leukocytes, 1 per cent large lymphocytes, 9 per cent small lymphocytes, 3 per cent mononuclear leukocytes and 27 per cent eosinophils. Bleeding time, clotting time and clot retraction were

normal. The prothrombin content was 100 per cent, or normal. During the patient's hospitalization the leukocyte count increased gradually to 29,000 and the ratio of eosinophils to 60 per cent. The increase in number of leukocytes was mainly due to the increase in eosinophils. There was complete absence of primitive or juvenile forms in the blood, but a considerable number of large monocytic lymphocytes was noted, just as may frequently be seen in chronic hyperplasia in the lymph-angioendothelial system.

Sternal puncture yielded marrow with 18 per cent polymorphonuclear cells, 8 per cent lymphocytes, 1 per cent monocytes, 19 per cent eosinophils, 27 per cent eosinophilic myelocytes, 11 per cent eosinophilic metamyelocytes, 1 per cent neutrophilic myelocytes and 2 per cent myeloblasts. The high percentage of primitive eosinophilic granulocytes (38 per cent) with a normal proportion of erythroblasts was characteristic for the bone marrow findings.

In the stools, on repeated examination, only intestinal trichomonads and cysts of trophozoites of Endamoeba coli were found.

Microscopic sections of specimens from the gastrocnemius muscle showed no evidence of trichinosis.

The ascorbic acid level of the blood serum was low, 0.11 mg. per hundred cubic centimeters. Plasma proteins and urea clearance were normal. Cultures of blood and urine revealed no organisms. Agglutination tests for typhoid, paratyphoid A and B and dysentery and tests for the heterophile antigen gave negative results. The basal metabolic rate was +27 per cent.

While the patient was hospitalized there was no essential change in the aspect of the cutaneous eruption except for the appearance of new hemorrhagic lesions, mainly on the back. The temperature was 99 to 100 F. Lately within the area of giant edema of the face and neck it has been possible to distinguish circumscribed hard infiltrates. Frozen sections from these infiltrates show perivascular infiltration and infiltrates of cells forcing themselves between the collagenous fibers.

Treatment has consisted of roentgen ray irradiation of the spleen with gradually increasing doses from 30 r upward.

DISCUSSION

DR. STEPHEN ROTHMAN (by invitation): The original appearance was that of a purpuric urticaria. Concerning the possible connection with injurious effects of organic solvents it may be mentioned that Lignac reported on experiments in which injections of benzene into mice caused changes in the blood similar to eosinophilic leukemia.

NOTE.—One Dec. 9, 1941 biopsy of a specimen from lately developed infiltrates showed vessel changes compatible with the diagnosis of periarteritis nodosa.

A Case for Diagnosis (Granuloma Annulare? Porokeratosis?). Presented by DR. S. W. BECKER.

J. O., a 13 month old boy, weighing 6,405 Gm., born in Indiana of Mexican and American extraction, has been hospitalized for observation for the past three months. At the age of 6 months the child had "red areas on the body which he would scratch. Sores developed on his back and buttocks." There was a history of retarded growth and development, failure to gain weight and inadequate diet.

Physical examination revealed a thin, poorly nourished baby, with an appearance suggestive of hypothyroidism: puffy eyelids, flat nose, tongue between lips, wrinkled ear, short neck and large abdomen. A pronounced funnel chest and slight flaring of the anterior ends of the ribs were noted. The spleen was palpable but not enlarged. The reflexes were hyperactive.

Dermatologic examination revealed sharply demarcated annular and serpiginous papulosquamous plaques, symmetrically located on the extensor surfaces of the knees and on the flexor surfaces of the forearms near the wrists. The papulosquamous border was distinctly infiltrated.

During the three month observation period, some of the original lesions have undergone spontaneous involution with residual hyperpigmentation. New lesions have appeared on the extremities.

A fluctuating temperature, which has reached 40 C. (104 F.) on occasion, was only partially explained by a transient infection of the upper respiratory tract. For the past week the temperature has remained below 38 C. (100.4 F.). There has been no significant gain in weight despite an adequate diet reenforced by additional vitamins. An iron deficiency (nutritional) anemia has been corrected. Thyroid medication was instituted two months ago. New cutaneous lesions have appeared despite treatment.

Urinalysis showed an occasional trace of reducing substance. A blood count showed a hypochromic microcytic anemia on admission but is now normal except for showing a mild leukocytosis. The Kolmer and Kahn reactions of the blood serum were negative. The cholesterol content of the blood was 322 mg. per hundred cubic centimeters, the serum calcium content was 10.1 mg. and the serum phosphorus content 4.6 mg.; the bleeding time was four minutes and the clotting time two and one-half minutes. Culture of the blood showed no organisms. A tuberculin test with 0.01 and 0.1 mg. gave negative results. A nasal smear showed no acid-fast organisms. A roentgenogram of the chest showed clear pulmonary fields, and roentgenograms of the skull, skin and extremities showed no abnormalities.

Histologic examination showed the changes to be predominantly in the epithelial structures. The stratum corneum was thickened and in places parakeratotic, and indentations and sweat gland orifices had a hyperkeratotic lining. The stratum granulosum and mucosum were thickened. The deeper sweat gland ducts were also hyperkeratotic and in places parakeratotic. There was slight perivascular round cell infiltrate. One specimen showed a single large collection of epithelioid cells.

DISCUSSION

DR. F. W. LYNCH, St. Paul: I prefer the diagnosis of granuloma annulare, in spite of the absence of typical histologic changes.

DR. S. W. BECKER: When I first saw this boy I thought he had granuloma annulare; however, the sections showed little change in the dermis but tremendous thickening and hyperkeratosis of the epidermis. Finally a section was obtained with one group of tuberculoid cells. None of the other possible diagnoses, such as lepra, sarcoid or any type of tuberculous disease, is tenable, because the lesions would certainly not have cleared as some of these plaques have. This child has many peculiarities. The pediatricians have not been able to increase his weight by any means they have tried, such as a full diet with vitamins of all sorts. I think that since the lesions have cleared, granuloma annulare is the diagnosis of choice.

A Case for Diagnosis (Trichorrhexis Nodosa?). Presented by DR. DAVID KAHN (by invitation) and DR. S. W. BECKER.

M. M., a 23 month old girl, born in Chicago, of Mexican extraction, in good general health, was brought to the clinic because of brittleness of the scalp hair. Until the age of 4 months, the patient had short thick curly hair, which frequently broke off. At the age of 4 months, the hairs fell out in the occipital region, then on the sides and finally on the vertex of the scalp. Regrowth was uneven, and in general the hairs were much shorter than they had been previously and remained brittle. The scalp had always been dry but not scaly. No erythema, pustules or crusts had been noted. The diet had apparently been adequate. No similar disease exists in the family.

The scalp is dry and presents follicular hyperkeratotic papules. The hairs are black and curly. Many hairs are brittle and short.

Histologic examination revealed nodular enlargements along the hair shafts with frequent longitudinal splitting of the hair at the nodes. No fungi were found in a potassium hydroxide preparation or on culture.

Treatment has consisted of 25,000 U. S. P. units of vitamin A daily (percomorph liver oil) and pine tar and salicylic acid ointment.

DISCUSSION

DR. NORMAN TOBIAS (by invitation), St. Louis: I thought the condition was trichorrhexis nodosa with typical brushlike nodosities, though I did not see the hairs under the microscope. The condition is usually acquired. Many women are unaware of the disorder until beauty technicians call it to their attention.

DR. MAURICE OPPENHEIM (by invitation): The clinical and histologic examinations reveal that the case is one of trichorrhexis nodosa.

DR. S. W. BECKER: When I first saw this child I thought it had monilethrix. We have never been able to demonstrate on several examinations the peculiar fusiform enlargement in the hairs characteristic for this disease. All we can say is that the disease may be trichorrhexis.

BROOKLYN DERMATOLOGICAL SOCIETY

SEYMOUR H. SILVERS, M.D., *President*

M. M. ESTRIN, M.D., *Secretary*

Oct. 20, 1941

Pemphigus Vulgaris (In Seborrheic Areas Chiefly). Presented by DR. H. L. FEIGENBAUM.

P. F., a man aged 77, married, born in Russia, was admitted to Kings County Hospital on Sept. 20, 1941, complaining of a bullous eruption on the chest and back. During the summer of 1940 the patient had a "chafing" and itching eruption in his groins, between his legs and on the chest. This cleared in about four months under treatment. About four months ago the patient noticed a vesicular and bullous eruption unlike the one he had the year before. It involved chiefly the chest and the back along the spine. This was accompanied by a loss of 15 pounds (7 Kg.) in weight and some pallor.

On admission the patient presented a bullous eruption confined almost exclusively to a triangular area on the chest with the apex of the triangle pointing downward and to an area bordering the spinal column from the interscapular region to the sacrum. This area was wider in the lumbar than in the dorsal region. The bullae, as a rule, were tense and filled with clear or turbulent fluid. Occasionally isolated bullae were seen on the trunk, usually in the midline. There were no lesions in the mouth, but the lower lip presented a few small healing bullae. At present there are still no lesions in the mouth, but the bullae are beginning to invade the areas contiguous to the seborrheic areas previously mentioned. The general condition of the patient is fair.

The reaction to a Pels-Macht test was 61 per cent. The results of chemical examination of the blood were normal; the sodium chloride content was 305 mg. per hundred cubic centimeters of serum. The histologic picture was reported to be compatible with a diagnosis of pemphigus vulgaris.

DISCUSSION

DR. JOEL SCHWEIG: According to the history, this patient has had the eruption for the past four and one-half months. I should have expected to see the man's health more seriously affected than it appears to be. The significant factor is that the eruption is predominant in the areas of seborrheic distribution; it seems to run a slow and benign course. Of late, reports in the literature, as well as case presentations at society meetings, leave the impression that pemphigus might have changed its malignant form to a more benign one. I wonder whether this impression will be supported by future statistical reports.

DR. M. DICKMAN: Clinically this case may be accepted as one of pemphigus, regardless of the absence of lesions in the mouth. I have frequently observed cases in which the general health of the patient was not affected early in the course of the disease.

DR. A. WALZER: I accept the diagnosis, but I think Dr. Schweig's conception of pemphigus vulgaris is too liberal. Pemphigus vulgaris means death. There is no pemphigus from which a patient gets well. Dr. Schweig probably refers to a certain bullous dermatitis which sometimes simulates pemphigus, and this condition is curable, but pemphigus vulgaris always is fatal, though it may run a milder course temporarily.

DR. L. CHARGIN: I wish only to remark on the presence of pemphigus in the mouth. I think it is time dermatologists stopped making oral lesions essential for a diagnosis of pemphigus. A considerable number of patients with pemphigus die without having had lesions of the mouth. Generally, when lesions are present in the mouth the disease is more rapidly fatal. Lesions on the body which are sufficiently characteristic are enough to base a diagnosis on.

Urticaria Pigmentosa, Psoriasis and Arthritis. Presented by DR. ABRAHAM WALZER.

W. A., a man aged 55, married, a barber, presented himself at the dermatologic clinic of the Brooklyn Jewish Hospital for a generalized rash of about eighteen months' duration. There was no history of any disease of the skin in his family. About two years ago pains developed in his right ankle, right fourth and fifth toes and left middle finger, for which he is at present being treated in the orthopedic clinic of the Jewish Hospital. Roentgenograms of these joints were made, and a diagnosis of infectious arthritis was made.

Now the patient shows the following features: 1. There is a generalized disseminated eruption of irregular patches, which are rounded or oval, not elevated, pea sized or a little larger, brownish and not pruritic and which on being scratched become red, raised and itchy; none of the glands, such as those in the axillas or groins, is palpable. 2. On the head of the penis and in the upper part of the gluteal fold are spots of typical psoriasis (duration not known); the nails of three or four fingers show the typical whitish detachment of the nail plate of psoriasis at the free edges. 3. The left middle finger (middle joint), right ankle and right fourth and fifth toes are swollen, tender and painful.

A histologic examination of a lesion removed from the left arm showed the typical picture of urticaria pigmentosa, with a tremendous number of mast cells.

DISCUSSION

DR. ABRAHAM WALZER: The interesting question that presents itself in this case is the relation between psoriasis and arthritis and the relation of both of these conditions to urticaria pigmentosa. The history of the duration of psoriasis in this patient is not clear, and the association of the psoriasis with the attacks of arthritis is not definite. In other words, there is no history of an interplay between these two conditions. In cases of psoriasis arthropathica the interplay is fairly definite. In such cases the treatment of psoriasis often improves the arthritis.

DR. M. E. GOEBEL: I do not know whether changes of the nails as described here are typical of psoriasis. It is not advisable to make a diagnosis of psoriasis on such changes alone.

DR. M. J. CANTOR: It is possible to make a diagnosis of psoriasis on lesions of the nails alone when the psoriatic plaque is subungual; the nail itself does not have to be involved; it may be only discolored. Pitting of the nails is not pathognomonic of psoriasis.

DR. S. HECHT: I cannot say whether this patient's arthritis is due to psoriasis or whether it appears concurrently. It is known that arthritis may occur with psoriasis. I also feel that one can make a diagnosis of psoriasis from lesions of the nails alone, even if other manifestations of psoriasis are absent.

DR. L. CHARGIN: I do not see such great difficulty in making a diagnosis of psoriasis from the nails alone. It is hard to tell a psoriatic nail when the nail is destroyed. But if one sees the primary papules underneath the nail and the raised edge on one side, a diagnosis of psoriasis is possible.

DR. I. N. HOLTZMAN (by invitation): The mast cell is seen in various inflammatory reactions; it is often seen in the connective tissue under normal conditions and is found in such diseases as tuberculosis and lichen planus. In urticaria pigmentosa there is a characteristic mass of these cells, particularly around the blood vessels. However, there are cases of urticaria pigmentosa in which there are no mast cells histologically but in which the clinical picture fulfils all the criteria of this disease. The pigment is brownish and is believed to be due to increased melanin.

Mycosis Fungoides. Presented by DR. MORRIS M. ESTRIN.

M. S., a man aged 52, entered Kings County Hospital in October 1939 because of a generalized eruption which had started in the spring of 1939 with lesions between the shoulder blades. He was given roentgen therapy, and the cutaneous lesions disappeared by January 1940.

In March 1940 there was a recurrence, and at that time the diagnosis of mycosis fungoides was suggested. The lesions were localized on the chest, back and arms and were red, patchy, infiltrated and itchy.

A biopsy in March 1940 showed a histologic picture of mycosis fungoides. Subsequent studies confirmed the diagnosis. Studies of the blood and urine gave normal results. The Wassermann and Kahn reactions were negative.

In March 1941 fungoid lesions developed, varying in size from that of a dime to that of a silver dollar, on different parts of the body. The ulcerating lesions healed slowly under cod liver oil ointment. During the summer of 1941 the patient received injections of a 2 per cent solution of sodium arsenate and additional roentgen treatment, with satisfactory results. Now he shows a few raised papular fungoid lesions scattered over the body.

DISCUSSION

DR. C. T. CHIARAMONTE: I agree with the diagnosis. The erythematous patches, with definite borders and beginning lesions on the abdominal wall confirm the diagnosis. I should like to inquire if any member has had any experience in treating this disease with iodized moogrol (a mixture of ethyl esters of fatty acids of chaulmoogra oils). I obtained no appreciable improvement in a case of advanced mycosis fungoides after administering this oil intragluteally.

DR. S. HECHT: I treated a patient with mycosis fungoides with this oil but could see no improvement.

DR. L. CHARGIN: Sodium arsenate is an old remedy used in the treatment of mycosis fungoides. It is an excellent arsenical to give by injection, and in mycosis fungoides arsenic is indicated. Arsenic attacks the disease from within; roentgen rays attack the disease from without only. The amount of roentgen rays given these patients must be controlled, for I have seen patients with mycosis fungoides treated by roentgen rays die, not from mycosis fungoides but from depression of the bone marrow. If the patient feels comfortable enough without roentgen rays, then this form of therapy should not be given and one should rely to a greater extent on other therapy.

Sarcoidosis. Presented by DR. JACOB SKEER.

D. V., a Negress aged 27, born in the United States, came to the dermatologic clinic of the Brooklyn Jewish Hospital on March 19, 1941, complaining of lesions on the face, lower lip, arms and back of two years' duration.

On the right cheek is a coin-sized depigmented lesion which is infiltrated and firm on palpation and is not tender. The nodular area is twice as large as the depigmented area and is attached to the overlying skin.

On the lower lip, to the left of the median line, is an indurated nodular lesion with an excoriated surface, resembling a chancre. Several individual nodules which are depigmented are situated on the back of the neck, shoulders and arms. These lesions are elevated, firm and attached to the skin. The cervical and axillary glands are enlarged. After biopsy of a lesion on the right shoulder the condition was reported to be sarcoidosis.

The histologic examination showed the cells of the basal layer to contain large quantities of pigment. There was no acanthosis or parakeratosis. Within the papillae and the upper part of the cutis were dilated lymphatics and capillaries and about them a slight infiltration by small round cells and large mononuclear cells. The deeper portions showed circumscribed focal areas composed of confluent tubercle-like structures, consisting for the most part of numerous epithelioid cells with scattered small round cells, extending fairly deeply. The collagenous tissue of the deeper part of the cutis was edematous, with a fraying out of the collagen bundles throughout. Scattered elastic tissue strands were seen.

Roentgenograms of the bones of the hands were normal. Roentgenograms of the lungs showed considerable infiltration on both sides; the periphery of the root shadows was frayed out, and there appeared to be some fine increased density of both lungs. The findings about the roots were consistent with those noted in Boeck's sarcoid. Studies of the blood showed a hemoglobin concentration of 70 per cent, 3,940,000 red cells, a color index of 0.9, 4,750 white cells and a differential count of staff forms 10 per cent, polymorphonuclear leukocytes 40 per cent, eosinophils 1 per cent, basal cells 2 per cent, lymphocytes 40 per cent and monocytes 7 per cent. There were reactions to 1, 2.5 and 5 mg. of tuberculin given intradermally.

DISCUSSION

DR. C. T. CHIARAMONTE: I accept this diagnosis because of the roentgenograms and the histologic observations. At first I thought the lesion a little too deep for the Boeck type and thought it was the Darier-Roussy type of sarcoid.

DR. I. N. HOLTZMAN (by invitation): I think the sarcoid lesion should be considered as purely a reaction. Sometimes a definite sarcoid reaction is seen in leprosy. It can occur in other diseases.

Condyloma Acuminatum (Carcinomatous Changes?). Presented by DR. MAX DICKMAN.

G. McC., a Negro aged 38, is presented from Kings County Hospital. He stated that he had gonorrhea in the early part of 1939. His present condition began in the latter part of 1939 and has become progressively worse.

The glans is entirely covered, except around the frenum, by closely aggregated, tufted projections, some sessile and some slightly pedunculated. The free surface is dry and verrucous. In a few areas these tufts have been accidentally torn off by the patient, revealing a dry granulomatous base. There are a few hard discrete glands in both inguinal regions.

The Wassermann reaction in March 1940 was reported as plus-minus. Subsequent tests gave negative results.

DISCUSSION

DR. MAX DICKMAN: The patient has had a circumcision performed recently. When he was first seen, the lesion was diagnosed condyloma acuminatum.

DR. L. CHARGIN: This is not a case of acuminate warts. I should perform a biopsy and look for granuloma, even lymphogranuloma, and I should rule out syphilis. The possibility of cancer must be considered.

Lichen Planus. Presented by DR. LESSER M. FRUCHTBAUM.

M. McC., a man aged 30, of Indian parentage, complained of a generalized eruption of six months' duration, starting three weeks after he had begun to handle cement.

The patient gives a history of having had pains in the chest a year ago. He received several intravenous and intragluteal injections, the nature of the medication being unknown. He also took bromides and salicylates in the form of bromoseltzer and aikaseltzer.

The patient was confined at the Long Island College Hospital from the middle to the end of August 1941, during which time a gland from the axilla and a piece of skin overlying it were removed for histologic studies; the condition was reported to be mycosis fungoides.

The Wassermann reaction of the blood was negative, and several blood counts were normal. A patch test with the cement he handles did not produce any reaction.

At present the patient shows numerous multiform lesions consisting of excoriations, flat papules, spines and areas of brown discoloration on the trunk and the upper and lower extremities. There are also many violaceous ringlike and oval raised lesions distributed on the sides of the trunk, forearms and legs, below the knee. The spinous lesions are situated on the arms and legs. There are no lesions in the mouth, but the lips are somewhat scaly and grayish. The patient complains of severe itching. There has been no subjective or objective improvement in the past five months.

DISCUSSION

DR. L. M. FRUCHTBAUM: The enlargement of the axillary gland, I think, was due to scratching, though the pathologic report of the section was mycosis fungoides. The patient attributes his disease to his work with cement. During the second week of his stay at the hospital some one suggested the possibility of drug eruption because of his intake of bromides and salicylates for a long time. Clinically the picture is that of lichen planus. In this case, in which there is a discrepancy between the clinical diagnosis and the pathologic report, the clinical diagnosis should take precedence over the microscopic observations.

DR. I. N. HOLTZMAN (by invitation): I examined the slides, and my impression was that the histologic picture was compatible with lichen planus. However, I have encountered cases in which the lesions were lichen-planus-like histologically but on subsequent examination could be fitted in with a diagnosis of mycosis fungoides.

DR. L. CHARGIN: When an eruption gives a reasonably clearcut picture of lichen planus, one should not confuse it with mycosis fungoides. The two diseases do not occur in the same location.

NEW YORK DERMATOLOGICAL SOCIETY

J. GARDNER HOPKINS, M.D., *President*

A. BENSON CANNON, M.D., *Secretary*

Oct. 28, 1941

Acne Vulgaris in a Four Month Old Baby. Presented by DR. EUGENE F. TRAUB.

A. M., a boy aged 4 months, was first brought to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Oct. 27, 1941. The mother stated that the eruption on the child's face had been present almost from birth, new lesions constantly appearing.

Numerous tiny comedos and small pustules are present on both cheeks. A few tiny pitted scars are also present. The patient has received no treatment.

DISCUSSION

There was a general agreement with the diagnosis as presented.

DR. EUGENE F. TRAUB: The presence of small pitted scars should be pointed out to the parents; otherwise therapy is apt to be blamed if any scars remain.

Nonsuppurating Panniculitis (Weber-Christian). Presented by Dr. J. Frank Fraser.

E. H., a woman aged 43, married, born in Germany of German parentage, a housewife of temperate habits, has never had any serious illness. She has one healthy child, a boy aged 6 years. She had one miscarriage, which she attributed to a fall. There is no family history of tuberculosis, cancer or diabetes.

Ten years ago, after a direct trauma to the right arm, in the course of two or three weeks a hard lump appeared in the skin at the site of the injury. Four years ago a similar nodule developed on the left arm at the site of an injury. Both growths were excised under local anesthesia. There was prompt recurrence, and new growths appeared in other locations without a previous history of trauma. Three years ago a lump appeared in the skin on the posterior aspect of the left flank. After a year's duration this lump disappeared spontaneously, leaving a deep dimple.

With the exception of the cutaneous lesions there is no physical evidence of disease. The external aspects of both arms show scars from local excisions. Posterior to the right axilla there is a pea-sized hard lump which is freely movable and not attached to the skin. There is a thickened indurated area on the posterior aspect of the right shoulder measuring 3 by 1 cm. There is a similar indurated area measuring 5 by 1 cm. in the upper posterior portion of the right side of the chest. A dimple measuring 4 by 1 cm. is seen on the right side of the flank and represents the site of a former lesion. On the right scapula there is an area of complete atrophy of the subcutaneous tissue with an advancing margin of induration.

On histologic examination the following features were observed: 1. There was a thin layer of stratified squamous epithelium. 2. There was moderate edema immediately beneath the epidermis. 3. There were scattered lymphoid cells and hypertrophied reticulum cells (the latter not numerous). 4. In the deeper portions of the corium there were aggregates of lymphoid and plasma cells and occasional large cells with vacuolated cytoplasm. 5. Still deeper there were edema and slight necrosis of the connective tissue and fat. There were small areas of thickening in the interstitial tissue caused by proliferation of fibroblasts and reticulum cells. In these areas large vacuolated foamy cells were more conspicuous than they were in the lymphoid collections. Thus there was a tendency for the more superficial areas to contain lymphoid and plasma cells, while the deeper areas showed more of the connective tissue proliferation.

DISCUSSION

Dr. Howard Fox: I agree with the diagnosis, especially from the appearance of the peculiar smooth depressed saucer-like areas of atrophy. This is shown in recorded cases, such as 2 recently reported by Dr. Cummins, of Boston (Arch. Dermat. & Syph. **38**:415 [Sept.] 1938). The disfiguring scars in this case, I think, are due to unnecessary surgical intervention.

Dr. Frank C. Combes: I do not think trauma is the cause, but it may precipitate the lesions. I sometimes have wondered whether the cause was a hypoergic reaction to the tuberculous toxin in somewhat the same way sarcoid occurs. In some cases panniculitis histologically resembles hypodermic sarcoid.

Dr. George C. Andrews: I concur in the diagnosis. This case resembles 2 others I have observed of this disease. I have no suggestions as to the relation of trauma to the onset except that it is a common history.

Dr. Eugene F. Traub: I think that what Dr. Combes has said is true. If the history is correct, some of these lesions appeared spontaneously without trauma, but trauma may be a definite precipitating factor. The surgical intervention helps to prove that, for there was peripheral activity where the surgeon had traumatized the tissues and more nodules had recurred along the edges and at the ends of the excision wound. It is probably more likely that this was due

to the trauma of the operation, rather than to other factors, such as recurrence from an inadequate excision.

DR. J. FRANK FRASER: In regard to trauma, I interrogated the patient and concluded that there was not much in her story of injury to the arm, because a majority of the lesions developed spontaneously. In regard to the excisions, it is possible that all of the growths were not completely removed. This would account for the recurrence. I should like to have an expression of opinion from the members in regard to treatment. In my opinion radium therapy would be of no avail. As the lesions undergo spontaneous resolution, I think no treatment is indicated.

DR. GEORGE MILLER MACKEE: I have had no experience with roentgen ray treatment or radium treatment of panniculitis, nor have I seen any favorable reports in the literature. I should think that large doses would be contraindicated and that small doses would be ineffective.

DR. GEORGE C. ANDREWS: I have had experience with 1 case of lipogranulomatosis that occurred after the injection of insulin. The lesions presented a concave appearance and induration, as in this case, but the disease was not the progressive clinical type as in this case. That patient was not benefited by roentgen therapy. I also treated the patient I presented today who has lupus erythematosus and lipogranulomatosis with roentgen rays and radium, without benefit. My 2 cases, of course, are not in the same category as the case presented by Dr. Fraser. However, I do not believe that roentgen ray treatment would be beneficial in his case. Radiotherapy does not usually influence inflammations of the fat.

DR. J. GARDNER HOPKINS: The general impression is that this condition is a disease of the peripheral circulation and not a disturbance of fat metabolism. The fact that most of the patients are febrile would suggest an infectious origin. I should think the most helpful thing would be to look for infectious foci, for instance, in the teeth and tonsils. I do not know whether this would hold if the patient has no fever. In 1 case Dr. Miller had recently at the hospital there seemed to be a response temporarily to sulfanilamide, although the patient came to autopsy finally.

Granuloma Annulare. Presented by DR. J. FRANK FRASER.

I. R. V., a man aged 32, a physician, was born in the Philippines of Philippine parents. The family and personal histories are normal. The present eruption began seven years ago as a circular group of papules 1 cm. in diameter on the left wrist. This lesion followed shortly after an abrasion from contact with a wicker basket.

The picture today is that of an oval lesion, 7 by 8 cm., occupying the flexor and outer surfaces of the left wrist, with a border of pinkish colored aggregated papules, elevated about 0.5 mm. above the adjacent healthy skin, and showing clear areas of central involution.

The histologic examination showed a picture which harmonized with the clinical diagnosis of granuloma annulare.

DISCUSSION

DR. HOWARD FOX: This case shows that granuloma annulare may not always present the classic, well known picture. Some of this patient's lesions suggest ordinary lichen planus, but the duration of several years would tend to exclude this diagnosis and the histologic report would certainly do so.

DR. GEORGE MILLER MACKEE: I agree with the diagnosis. While the histopathologic observations are not distinctive, I think they are suggestive of granuloma annulare.

DR. FRED WISE: I agree with the diagnosis as presented.

DR. J. GARDNER HOPKINS: After a brief glance at the section I thought the histologic picture looked like that of sarcoid. It certainly did not look like

that of granuloma annulare. I should like to know what the impression of the other members was.

DR. EDWARD R. MALONEY: The condition does not look like granuloma annulare to me. It seems to me to be superficial. There is not much infiltration or induration. I do not know what it is, but I should not make a diagnosis of granuloma annulare.

DR. GEORGE MILLER MACKEE: That lesion began as a papule or nodule. It became umbilicated and spread peripherally, producing annular configuration. That is the typical evolution for granuloma annulare. Under the microscope there is some degeneration but not so much as one would expect in a lesion of such long duration.

DR. EDWARD R. MALONEY: Has this patient been treated? Has he had any roentgen ray treatment?

DR. J. FRANK FRASER: He has never had any roentgen ray treatment.

DR. HOWARD FOX: I do not see how any one could make a clinical diagnosis of granuloma annulare at present. It seems to me that Dr. MacKee's opinion is based on the history of a lesion which became umbilicated and then spread.

DR. J. FRANK FRASER: In regard to the histologic picture, I am satisfied that it fits better with granuloma annulare than sarcoid. The characteristic hard fibrous tubercles seen in sarcoid are not present. What one sees is epithelioid cells, giant cells and a tendency to necrosis, which is characteristic of granuloma annulare. If this condition is not granuloma annulare, what else can it be? Other conditions have been excluded.

DR. EUGENE F. TRAUB: Does granuloma annulare ever terminate with scar formation if it is not treated? Would a scar as part of the process exclude that diagnosis? That is the point I recently made, and I should like to know if the members agree. Has the condition improved any since the specimen for biopsy was taken? Frequently such intervention is followed by decided improvement.

DR. J. FRANK FRASER: No. The condition has not improved since the specimen for biopsy was taken. Has any one any suggestions for treatment?

DR. HOWARD FOX: I recommend the use of roentgen rays, which as a rule have a favorable action on both granuloma annulare and sarcoid.

Lupus Erythematosus and Lipogranulomatosis. Presented by DR. C. ANDREWS.

W. L., a woman aged 34, was previously presented before the New York Dermatological Society on Nov. 28, 1939 and before the New York Academy of Medicine, Section of Dermatology and Syphilis on Oct. 1, 1940 (ARCH. DERMAT. & SYPH. **41**:965 [May] 1940; **43**:726 [April] 1941).

Since the last presentation, treatment has been continued with germanin, injections of sodium iodide, and a bismuth compound, but there has been no improvement. The local condition has spread, and there is a noticeable change in the patient's general condition; she has grown weaker and has lost considerable weight.

DISCUSSION

DR. FRANK C. COMBES: I do not recall exactly what this patient looked like when she was presented here before. To my best recollection there does not seem to be very much change in the condition, but I cannot offer any other diagnosis than lupus erythematosus profundus. The part that interested me was the ulceration, which I understand was spontaneous. Of course, the skin is very thin, and there is considerable atrophy of the subcutaneous fat, which may account for the ulceration.

DR. FRED WISE: I do not believe that the term lupus erythematosus profundus is appropriate for this form of the disease. I should rather designate it

as a hyperkeratotic lupus erythematosus associated with an underlying lipogranulomatosis. This combination of two apparently unrelated diseases is unique in my experience.

DR. EUGENE F. TRAUB: I remember this case well because I thought it was most unusual and interesting when presented before. The presenter, I believe, said there were two microscopic examinations to prove the diagnosis of lupus erythematosus and that the other fatty changes had also been microscopically confirmed. I presume therefore that that excludes any other possible diagnosis, although I have some doubts because of the peculiar ridge or bandlike appearance and the absence at present of any scaling or telangiectasia, especially in the scalp. The latter may or may not be a necessary feature, as improvement in the process may have eliminated this (usually telangiectasia is fairly permanent, however). The changes in the scalp, the peculiar bandlike lesions, suggest some other condition. One of the conditions described as occurring in that location is bandlike circumscribed scleroderma. If the histologic examination has definitely excluded such a possibility, it excludes the only other possible diagnosis I can think of.

DR. PAUL E. BECHET: The boardlike hardness is somewhat suggestive of scleroderma, but this dermatosis has been ruled out by means of a histologic examination. There is no doubt in my mind that a rare variant of lupus erythematosus exists presenting a clinical picture resembling that in Dr. Andrews' case. I reported 2 instances of this variant before the American Dermatological Association at its meeting in New Orleans (Lupus Erythematosus Hypertrophicus et Profundus, ARCH. DERMAT & SYPH. **45**:33 [Jan.] 1942). In these cases, as well as in a few others that came under my observation, the objective symptoms were definite. The only variation in the clinical picture was the degree of severity of the lesions. The disease belongs to the fixed discoid variety. A typical example is characterized by more or less oval, rather sharly outlined, greatly elevated, plateau-like plaques, with indurated rolled borders of violaceous to dull red.

The surface of the plaque is at times covered with thick adherent scales. The center of the plaque is depressed, and extensive scarring, occasionally cribriform, is present. At other times the plaque is covered with thick, dry, digitate, hyperkeratotic layers. These oval plaques at times coalesce to form large elevated areas, as in Dr. Andrews' patient. This phase of lupus erythematosus is extremely rebellious to treatment, but I have observed resolution of lesions after the administration of a hundred or more injections of gold sodium thiosulfate in 100 mg. doses once a week, with frequent examinations of the blood and urine and frequent inspection for dermatitis or pruritus.

DR. HOWARD FOX: It is possible that there are two different diseases in this unusual case. Much of the eruption looks like lupus erythematosus, especially the lesions on the scalp. She also has lesions which do not accord with my conception of any type of lupus erythematosus. These may be lipogranulomatosis, as has been suggested. I do not know what therapeutic suggestions can be given as the presenter has tried almost every conceivable type of treatment.

DR. J. GARDNER HOPKINS: I question whether the diagnosis of lupus erythematosus can be made definitely on the histologic report. I do not doubt that the condition is lupus erythematosus, but I do question the stand that because the pathologist says this is lupus erythematosus, that is what it is.

DR. J. FRANK FRASER: I could not make a diagnosis of lupus erythematosus from the histologic picture.

DR. GEORGE C. ANDREWS: This ulcer appeared spontaneously as a small pustule at the center of the lesion, which opened and drained and formed a small sinus. It drained persistently and became an ulcer ½ inch (1.3 cm.) deep. Why it developed I have no idea, and it has persisted for over a year. The first biopsy was made at the Skin and Cancer Unit of the New York Post-Graduate

Medical School and Hospital, and the diagnosis was definitely lupus erythematosus. The patient's son has a sarcoid and is being treated at the same institution. Concerning changes in this patient since she was presented here last year, her general health has become much depleted. She has lost weight and does not look well. The lesions of the scalp did show some erythema a few months ago. Possibly some of the treatment has benefited those lesions. She was given sulfathiazole for a while, and it seemed to help. Lupus erythematosus profundus often extends through the entire cheek to involve the mucous membranes of the mouth. Perhaps the original diagnosis of lupus erythematosus and panniculitis is preferable. The first biopsy made at Vanderbilt Clinic showed much more resemblance to lupus erythematosus than the last one did.

A Case for Diagnosis (Extracellular Cholesterosis? Granuloma Fungoides?). Presented by DR. J. GARDNER HOPKINS.

R. A., a woman aged 59, an occupational therapeutist, is presented for Dr. Beatrice M. Kesten. Eczematoid patches developed on the elbow and the dorsa of the hands two and one-half years ago. New lesions have gradually developed on the arms, the dorsa of the hands, the lower extremities, the lower portion of the abdomen and the midportion of the soles, which are now studded with reddish brown discoid lesions, 1 to 4 cm. in diameter; some are weeping, some scaling and all moderately infiltrated. On the face, including the mucocutaneous junctions, are a few red, scaly, infiltrated lesions about 4 mm. in diameter. They are painful on friction and itch intermittently. There has been no fever, and she has no definite extracutaneous symptoms. About the time of onset the patient had some pain and cramps in her feet, which seemed unrelated to the cutaneous trouble. Recently she says she feels sick and finds carrying on her work increasingly difficult.

On physical examination there was no detectable enlargement of the lymph nodes, liver or spleen and no other significant findings except some infected teeth, which have been extracted. The blood count, the chloride and nonprotein nitrogen content of the blood and the basal metabolic rate were within normal limits. The one striking finding was a serum cholesterol content of 352 mg., 388 mg. and 270 mg. per hundred cubic centimeters, on three occasions (normal, 160 to 220 mg.). On the third examination the free cholesterol amounted to 87 mg. per hundred cubic centimeters, the ratio of esters to free cholesterol being 1.97.

Three histologic examinations have shown similar changes in varying degree. There were acanthosis and parakeratosis with edema and extensive vesiculation of the epidermis, some vesicles containing only mononuclear cells and others polymorphonuclear cells. The striking change was a rather massive accumulation of lymphocytes and histiocytes filling the reticular layer of the corium and extending up into the elongated edematous papillae and down around the blood vessels of the upper part of the reticular layer. The protoplasm of the histiocytes was foamy, suggesting the presence of lipid, and their borders were indistinct, but sections stained with scarlet red showed little demonstrable fat. There were, however, striking collections of fat droplets in the walls of the capillaries of the papillae, apparently in the endothelial cells. No anisotropic bodies were seen under polarized light.

Analysis of a sample from a cutaneous lesion by Dr. Homer Kesten showed: total cholesterol, 260 mg. per hundred grams wet weight (normal control being 80 mg.); free cholesterol, 190 mg. per hundred grams wet weight (normal control being 60 mg.), and ratio of esters to free cholesterol, 0.37.

The failure to demonstrate this excess histologically could be explained on the hypothesis that the cholesterol was emulsified with protein and not with other lipids, as is usually the case.

The patient's general health has been good except for hay fever and severe asthma. She is hypersensitive, according to cutaneous tests, to a number of foods.

as well as to dust, feathers, horse dander, timothy pollen and staphylococcus. Her asthma has been completely controlled by desensitization. She has had scarlet fever, typhoid fever and catarrhal jaundice. Cervical lymph nodes (believed to be nontuberculous) were excised at the age of 22. She had an appendectomy at the age of 24 and a tonsillectomy at 52. She takes few medicines, no bromides or iodides and she has taken a phenolphthalein-containing preparation only on rare occasions but not recently.

Fig. 1.—A case for diagnosis; infiltrated placques on the forearms.

Since the patient has been on a low cholesterol diet and taking soy bean lecithin (containing choline and inositol), in three weeks the serum cholesterol has dropped 100 mg. and the lesions have appeared flatter. This therapy has been continued, however, together with the filtered roentgen rays. No lesions have disappeared, although some are flatter. New lesions have appeared. Treatment has been ineffective. Various local applications have seemed only to aggravate the condition. Three courses of fractional unfiltered roentgen rays (total about 1,200 r) have caused temporary improvement followed by exacerbation. More recently, 2 additional skin units of filtered roentgen rays have been given to most lesions without particular benefit (800 r through 2 mm. of aluminum).

A diagnosis has seemed difficult. There is some clinical similarity to the condition described by Urbach and by Laymon as extracellular cholesterosis, although this patient's lesions are not orange or yellow. The infiltration of the upper part of the cutis suggesting a reticuloendotheliosis and also vesiculation of the epidermis were noted in Urbach's and Laymon's cases. Urbach found the cholesterol content of lesions from his patient five times that of normal skin and in early lesions observed a heavy deposit of lipid material about the blood vessels. On the other hand, both observers demonstrated extensive extracellular deposits of lipids in sections from older lesions, and both reported the serum cholesterol not elevated. The histologic picture is compatible with a diagnosis of granuloma fungoides. However, the distribution and eczematous character of the lesions and the resistance to roentgen ray therapy are somewhat against it. Moreover, the striking

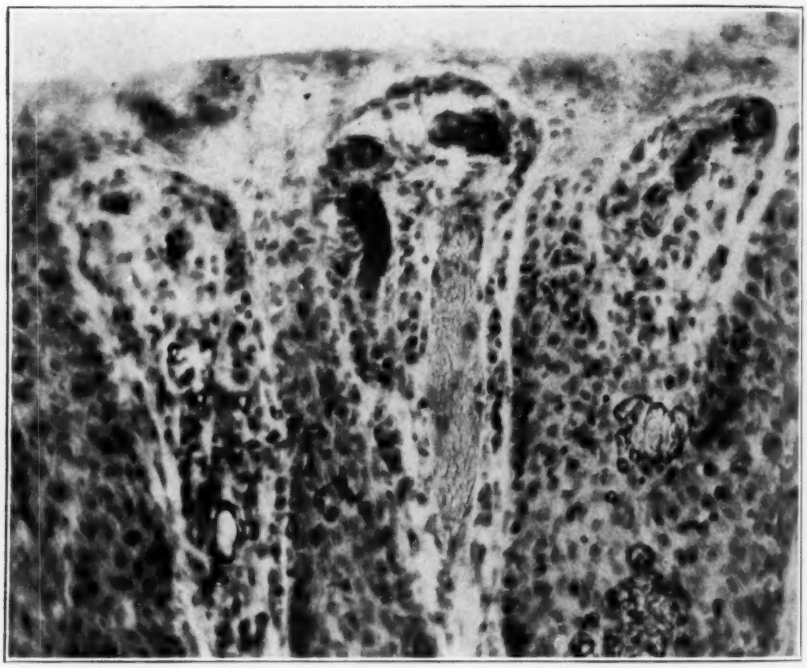

Fig. 2.—A case for diagnosis; photomicrograph of tissue from lesion on the thigh, showing fat (scarlet red stain).

hypercholesteremia and the high cholesterol content of the skin are not known to be characteristics of granuloma fungoides.

DISCUSSION

DR. A. BENSON CANNON: I am accustomed to thinking of mycosis fungoides as a dry process and of the lesions being varied in types. The nodules in this case are bright red and edematous with exudation and crusting, a condition that I would not associate with mycosis fungoides. While I am not sufficiently acquainted with cholesterosis to express a definite opinion, I believe that the uniform size of the nodules in this case more nearly conforms to that seen in cholesterosis, and I would make that diagnosis provided iodides and bromides could be excluded as possible causes.

DR. PAUL E. BECHET: There is a possibility that the iodides might be responsible for this eruption. The patient might have used iodized salt for a long time, thus becoming sensitized to small doses of iodine taken internally. Such an incidence is not uncommon, as in my experience iodized salt taken for a long time may cause a hypersensitivity which flares up into a more or less serious dermatosis after the administration of even a few drops of potassium iodide for a day or two. One patient under my observation nearly died from a severe gangrenous papulobullous generalized eruption, which began after the ingestion of 40 to 50 grains (2.5 to 3 Gm.) of sodium iodide in a few days. He had been using iodized salt for years. Free iodine was found in his urine (Bechet, Paul E.: Iodized Table Salt as an Etiologic Factor in Iododerma, ARCH. DERMAT. & SYPH. **29**:529 [April] 1934).

DR. JEROME KINGSBURY: I too feel that dermatitis medicamentosa should be excluded before consideration is given to the diagnosis of mycosis fungoides.

DR. J. FRANK FRASER: The first thing I thought about on looking at the lesions in this case was iododerma. I strongly oppose the view that this condition is mycosis fungoides. In the first place, none of the lesions is characteristic, even in gross appearance. There might be some isolated lesions which bear some resemblance to those of mycosis fungoides. The location on the extremities, with none on the back or chest, and the weeping of the lesions are against this diagnosis. In regard to the histology, mycosis fungoides can be excluded. With one exception (distribution of the exudate), all the characteristic histologic features are absent. The diagnosis rests between a drug eruption and extracellular cholesterosis.

DR. J. GARDNER HOPKINS: Bromoderma and iododerma have been excluded as far as possible by the history.

DR. HOWARD FOX: The evidence brought out in the discussion is against mycosis fungoides. There is also evidence against a halogen dermatitis. The appearance of the lesions is not that of either bromoderma or iododerma, and the lesions are neither painful nor tender. By exclusion this makes the suggestion of the presenter more tenable, that this case is one of extracellular cholesterosis.

DR. GEORGE C. ANDREWS: I agree with the diagnosis of extracellular cholesterosis. The condition certainly looks like the picture of that disease in Urbach's case, and the histologic picture does also. I have here a quotation from Urbach's description of the histologic picture which says: "It is a severe injury to the endothelial lining of the blood vessels . . . but above all an infiltration of lipoid which starts about the vessels and spreads to involve the entire cutis." Certainly that is what this slide shows, a lipoid infiltration about the small capillaries in the papillae.

DR. GEORGE MILLER MACKEE: If the eruption were due to bromine or iodine there should be pustular, bullous or vegetating lesions or a combination thereof. Mycosis fungoides must be considered because it is well known that conditions which are diagnosed as eczema or psoriasis do eventuate, at times, in mycosis fungoides. However, the histologic structure is not that of mycosis fungoides, and the distribution is not typical of this disease. The fact that the lesions do not respond readily to roentgen ray treatment is against the prefungoid stage of mycosis fungoides. The eruption looks more like that variety of eczema called chronic discoid lichenoid dermatitis, but this condition is seen mostly, if not entirely, in male Jews. The lipoid deposits are interesting. Not a great deal is known about lipoid deposits in the inflammatory dermatoses. I remember a case of pustular psoriasis in which there was a high cholesterol content in the blood and in the pustules. The eruption certainly resembles that described by Urbach. I am inclined to agree with the diagnosis of extracellular cholesterosis.

DR. R. H. RULISON: As Dr. MacKee has said, one cannot ignore this high cholesterol value. This woman happens to be a family friend whom I have known for years. If she were not in such excellent hands, I would be much more

impressed with the diagnosis of a drug eruption. She has been asthmatic for years. Of course in asthmatic patients who go here and there for help, it is likely that iodides and other drugs were tried, but that would not explain the abnormally high cholesterol values. I am inclined to accept the diagnosis of extracellular cholesterosis. I do not think she has mycosis fungoides.

DR. FRED WISE: While I do not feel competent to submit an opinion on the histopathology, I would commit myself to the clinical diagnosis of extracellular cholesterosis. There is a striking similarity between the groups of lesions on the flexor aspect of the right forearm and the manifestations of almost identical character in the cases published by E. Urbach (*Klin. Wchnschr.* **13**:577, 1934) and by C. W. Laymon (Extracellular Cholesterosis, ARCH. DERMAT. & SYPH. **35**:269 [Feb.] 1937). I am not in accord with the opinion expressed by some of the members that the eruption resembles mycosis fungoides, idiopathic eczema or a drug eruption.

DR. EUGENE F. TRAUB: In the absence of a history of drug ingestion it seems that the possibilities may still be narrowed down to the two tentative diagnoses presented, with emphasis on the cholesterosis. The textbook illustrations which Dr. Andrews showed me appeared similar to the picture this patient presents, and the histologic picture favors that diagnosis. The only feature which struck me as unusual was the one lesion on the ankle in which a number of these soft infiltrated lesions had coalesced to form a horseshoe-shaped lesion. That was the only lesion I could find on the patient which showed a definite configuration of this character, which is one of the characteristics seen in mycosis fungoides. That one lesion keeps me from accepting unequivocally the diagnosis of extracellular cholesterosis.

Granuloma Annulare. Presented by DR. FRED WISE.

J. G., a girl aged 2 years, referred by Dr. Charles K. Good, was admitted to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 30, 1941 presenting cutaneous lesions of one year's duration. The child appears to be in good health and is unusually active. There are no subjective symptoms. Her mother noticed the first two papules on the middle of the dorsal surfaces of the feet at about the same time. Later similar lesions developed on the legs, and during the past six months, on the hands and wrists. The evolution of the patches, as carefully observed by the mother and borne out by examination of the lesions, shows that they were of three types. Some of them appeared as solid, pea-sized to larger, flat-topped nodules. These slowly but steadily spread peripherally with central clearing, thus forming discoid plaques with clearcut round centers, which seemed to consist of normal skin with no evidence of atrophy. Other lesions developed into solid, round and oval patches, while still others spread in a rounded bandlike manner to form incomplete oval rings. The lesions never underwent regression.

The distribution of the lesions is roughly symmetric; there are about thirty, varying in size from 1 to 7 cm., and located on the dorsal surfaces of the hands and wrists, on the extensor surfaces and sides of the lower half of each leg, in the region of the achilles tendon, on the extensor surface of the left great toe and on the dorsal aspects of the feet, extending from the latter area to the inner borders of the soles for about 2 cm. All are sharply demarcated, raised about 1 mm., dull red, with a purplish hue, nonscaly and nontender. Most of the lesions have even flat tops throughout; some have a distinct, raised, fairly even border of about 2 mm. Others, such as the crescentic lesion on the dorsal surface of the right hand, have an irregular rounded surface consisting of partially coalesced papules which still retain their individual identity. Most of the lesions are discrete, but a few are bound edge to edge, thus giving a beaded appearance. On diascopic pressure the plaques are easily compressible, leaving a yellowish tint and exposing small capillary loops.

Physical examination, including a roentgenogram of the chest, showed no abnormalities. The hemogram showed 65 per cent lymphocytes and 28 per cent polymorphonuclear leukocytes. Mycologic examination and culture of material from a plaque on the hand were negative.

A histologic section examined by Dr. Charles F. Sims was reported as follows: The epidermis was mildly irregular with rather short anastomosing rete pegs. There was mild hyperkeratosis. The cutis presented a moderate interstitial and in part parenchymatous edema of the collagen. The vessels of the upper and middle parts of the cutis were moderately dilated, their walls somewhat edematous, and surrounded by a sparse cellular infiltration composed of small round and occasional wandering connective tissue cells. The collagenous framework surrounding the vessels was lacy and poorly stained. In the midcutis were two areas in which the aforementioned cellular infiltration was arranged in an arciform manner. The findings were insufficient for a definite diagnosis but were suggestive of granuloma annulare.

The patient showed paradoxic reactions to intracutaneous injections of old tuberculin: plus-minus to a dilution of 1 : 1,000,000, 1 plus to a dilution of 1 : 100,000 and plus-minus to a dilution of 1 : 10,000. Moro's patch test (50 per cent of old tuberculin and hydrous wool fat) gave a negative reaction.

DISCUSSION

DR. HOWARD FOX: From the clinical standpoint this eruption is typical of granuloma annulare, in my opinion.

DR. GEORGE C. ANDREWS: I think that clinically this condition looks typical of granuloma annulare, but microscopically there are changes which Dr. Hopkins pointed out to me that certainly suggest another disease. I should like him to discuss that point.

DR. HANS J. SCHWARTZ: I think too that clinically this eruption is granuloma annulare.

DR. A. BENSON CANNON: I agree with the diagnosis of granuloma annulare.

DR. J. GARDNER HOPKINS: On looking at the section I did not see any evidence of granuloma. There was considerable hyperkeratosis, which dipped down into the surface of the epidermis, and there were one or two sweat glands filled with keratotic plugs. The picture suggested porokeratosis. I looked again at the child after seeing the section but did not see any ridges. However, the disease is of long duration, almost all of the child's life. I certainly suggest that further biopsies be made and that point of view be considered.

DR. FRANK C. COMBES: I did not see the microscopic section, but clinically this condition is typical of granuloma annulare. Its symmetry is a little unusual. I do not think it is Darier's erythema annulare centrifugum, although in certain characteristics it resembles it. Even considering the similarity of the histologic picture to porokeratosis, I do not see any clinical characteristics of that disease. There is no atrophy or peripheral ridge.

DR. GEORGE MILLER MACKEE: Clinically I think the condition is granuloma annulare. I did not see the slide. I should not make a diagnosis of porokeratosis for reasons which have just been given.

DR. R. H. RULISON: I thought that clinically the case was one of granuloma annulare.

DR. EUGENE F. TRAUB: Considering the two conditions suggested, there is certainly no doubt that clinically the condition in this case is granuloma annulare. Porokeratosis is radically different in appearance and is exceedingly rare, by the way. The lesions in this case are absolutely different from those of porokeratosis. My idea about the histology is that the section was cut from an area of skin that happened to be atypical.

DR. FRED WISE: An unqualified microscopic diagnosis of granuloma annulare is as a rule obtained in the classic forms of the disease when it occurs in isolated, sharply defined, oval or discoid lesions on the dorsum of the hand or on the cheek near the ear. However, in the disseminated variety, most often encountered in infants and young children, the histologic observations are frequently vague and not decisive. In such instances the report more often implies that the histologic picture is merely suggestive of granuloma annulare and that a definite microscopic diagnosis cannot be made on the basis of a single histologic examination.

DR. PAUL E. BECHET: Close observation of the rectangular patch on the back of the right hand shows a border made up of conglomerate incomplete rings typical of granuloma annulare. I agree entirely with Dr. Fox that clinically the condition is granuloma annulare. In a case of proved porokeratosis the clinical picture is entirely different.

Xanthoma Tuberosum Multiplex. Presented by DR. EUGENE F. TRAUB.

F. V., a woman aged 55, was first seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Oct. 6, 1941. She presented numerous yellowish, cherry-sized, raised, firm, rounded and oval plaques and tumors on the elbows, hands and lip. Some of the nodules were gritty on palpation. She complained of a burning sensation in the mouth. Lesions on the palms and fingers were linear and located along the lines of cleavage.

The Wassermann and Kahn reactions of the blood were negative. The urine was normal. Chemical examination of the blood showed 12.5 mg. of urea nitrogen (normal 10 to 15 mg.), 2.1 mg. of uric acid (normal 2 to 4 mg.), 490 mg. of chlorides, as sodium chloride (normal 450 to 500 mg.) and 125 mg. of sugar, true dextrose (normal 60 to 100 mg.) per hundred cubic centimeters. The cholesterol content of the blood was 355 mg. (normal 160 to 230 mg.) per hundred cubic centimeters.

Histologic examination showed a soft fibroma. The section showed a practically normal epidermis with a thick nonparakeratotic scale. The midcorium was filled with a mass of cellular connective tissue cells in whorls and strands between broken fibers on noncellular connective tissue.

The patient is presented principally for therapeutic suggestions and specifically to obtain an opinion as to the advisability of removing the larger tumors on the elbows. Because of the decided fibrosis present, I should like to know if there is any danger of keloid formation on removal.

DISCUSSION

DR. A. BENSON CANNON: I recommend excision of the lesions, believing that there is no more likelihood of a recurrence or keloidal growth than from the removal of any other lesion.

DR. HOWARD FOX: All will agree that dietary measures are of no permanent value in this disease. It is entirely proper, I think, to excise these lesions, as has often been done with success and without the formation of keloids.

DR. GEORGE MILLER MACKEE: My impression is that these lesions can be removed surgically without recurrence and rarely, if ever, with hyperplastic scar formation. Usually just the opposite occurs. There is often an atrophic scar. Immediately after excision the scar may be threadlike, but a few weeks later it is likely to broaden and wrinkle. Even so, the patient is apt to be satisfied. The large number of lesions in any one area might make plastic surgery necessary. I think that surgery is preferable to destructive methods, such as solid carbon dioxide and electrodesiccation. With those methods the wounds last a long time and the scarring is apt to be considerable.

DR. FRED WISE: I agree with Dr. Fox and Dr. MacKee. Dr. Traub has shown a remarkable case of skin grafting on a previous occasion. I suggest that

in this case large areas be excised and grafted instead of the individual lesions being removed. Then one may avoid separation of the edges of the skin, which Dr. MacKee mentioned. I do not fear keloidal formation in this patient.

DR. EUGENE F. TRAUB: This woman is anxious to have the masses surgically removed, provided the members feel that that is the correct approach.

Dermatitis Lichenoides Chronica Atrophicans (Csillag). Presented by DR. PAUL E. BECHET.

M. C., a woman aged 60, presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, states that the eruption has been present for ten years and has increased slowly since its onset.

In the epigastric, hypogastric and inguinal regions and on the upper and inner surfaces of the thighs there are sharply defined patches varying in diameter from 2 to 10 cm. Some are raised; some are atrophic, and others are covered with fine scales. On the thighs the patches are shiny and silvery white. Other patches consist of small flat papules coalesced to form linear lesions which are so grouped as to form an irregular network, with apparently normal skin between the meshes.

Histologic examination revealed in the upper part of the cutis a number of small, somewhat swollen vessels arranged in groups. There was considerable edema in the subepidermic region. The overlying epidermis was flattened and showed no important change. The elastic tissue was missing in the subepidermic area.

The patient has glycosuria and hyperglycemia.

DISCUSSION

D. J. FRANK FRASER: I agree with the diagnosis as presented.

DR. FRANK C. COMBES: I agree with the diagnosis.

DR. FRED WISE: I am of the opinion that the term dermatitis lichenoides chronica atrophicans is a most appropriate designation for the eruption under discussion. In this patient there is no evidence of the existence of lichen planus in any of its varieties; in fact, there is a total absence of papular lesions. In lichen sclerosus et atrophicus of Hallopeau there are individual lichen-like, elevated and indurated papules, many of which show solid central plugs at their summits. In the late stages of Hallopeau's disease the papular elements flatten out and the neighboring lesions often fuse, resulting in depigmented, atrophic and sclerotic plaques of various sizes and shapes. Lichen planus atrophicus is readily differentiated from Hallopeau's disease on both clinical and histologic observations.

DR. J. GARDNER HOPKINS: I should like to know about treatment. Do conditions of this kind respond to roentgen rays?

DR. EUGENE F. TRAUB: These conditions are entirely unresponsive to any treatment.

Congenital Alopecia with Atrophy of the Nails. Presented by DR. EUGENE F. TRAUB.

M. N., a woman aged 28, first visited the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 17, 1941. She presented a total alopecia with atrophy of all the nails, both conditions having been present since birth. There was a slight amount of hair present at birth, which, however, soon fell out and has not regrown at any time except for a few straggling hairs and some slight fuzz. She also presented a total lack of hair in the axillas, pubis, eyebrows and eyelashes. A large number of the members of her family have had a similar condition. The past history is relatively unimportant, one of the chief illnesses having been jaundice as a child. A family tree is appended. The patient has had moderately severe keratosis palmaris et plantaris.

A roentgenogram of the skull showed no gross abnormality in detail or outline of the bones of the vault or base. The skull was normal except for close approximation of the clinoids and possible slight membranous infiltration of the left antrum. The basal metabolic rate was 6 per cent below the average normal.

Therapy has consisted of ultraviolet irradiation of the scalp, together with other stimulating local remedies.

Family Tree of Patient with Congenital Alopecia *

Francois B. + Elizabeth C. 0

1. Moise +
2. Benjamin +
3. David +
4. Telesphere 0
5. Mari +
6. Lucie 0
7. Emilie 0
8. Belanise 0 Jean Baptist G. +
9. Christine 0
10. Domitelle +

1. Delima +
2. Salome +
3. Malvina +
4. Theodore 0 Elsie G. +

Julien +
Otavie +
Elia +
Belense +
Joseph 0
Valerise 0
Judith 0
Christine 0

5. Joseph +
6. Valerise +
7. Caroline 0 Camile D. +

Herminise 0 Pierre B. +

Randolph +
Sylvia +
Theodore +
Leonoire +
Beatrice +
Raymond +
Emily 0

8. Christine 0 Jerimie R. +

Marie 0
Mabel +
Emily 0 Lester N. +

Marjorie 0 (patient presented)
Rivera +
Elizabeth +

Florence +

9. Helen 0
10. John 0

* The plus sign indicates hair and the zero, no hair.

DISCUSSION

DR. PAUL E. BECHET: It is unfortunate that the prognosis is so unfavorable. In the few cases that I have observed I have never noted any return of hair.

DR. FRANK C. COMBES: Is any one here sufficiently well versed in genetics to predict how long this will go on in the progeny of this patient?

DR. GEORGE C. ANDREWS: From a consideration of the family tree, the condition seems to be transmitted more by the males than by the females. One son

married, and four of his seven children had this condition. Each of the girls married, and only one of seven or eight children had the condition.

DR. GEORGE MILLER MACKEE: I think this condition is a congenital ectodermal defect. It has to be called minor, as compared with major ectodermal defects, and it is recessive in both male and female.

DR. FRED WISE: I agree that the prognosis is bad and treatment useless.

DR. EUGENE F. TRAUB: At the dermatologic clinic of the University of Vermont, patients with this condition are frequently seen, coming from a settlement of French-Canadians, where the disease is fairly common. This patient's family, interestingly enough, comes from that same territory. There is no intermarriage recorded in this family tree. The disease is a variety of congenital ectodermal defect.

A Case for Diagnosis (Lichen Spinulosus? Eczema?). Presented by DR. EUGENE F. TRAUB.

L. R., a boy aged 16, presented himself at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital in April 1940 with an eruption of about two years' duration. The eruption was grouped chiefly on his right side, where there were various-sized patches, measuring from 1 or 2 cm. to 5 or 6 cm. in diameter. These consisted of pinpoint-sized keratotic papules with slight pigmentation. Some of the lesions seemed to clear centrally with only scaling papules peripherally.

The eruption is chiefly on the trunk, although there are a few lesions on the face and neck and in the popliteal and cubital spaces and there is some eruption between the toes. In June 1940 there was some apparently spontaneous improvement, but the eruption has relapsed since then. The patient has received small doses of vitamins A, B and D in tablet form. He has received no roentgen ray treatments. Mycologic examination and culture of material from the toes showed no organisms.

Histologic examination of a lesion from the back was reported as "eczema." The section showed an irregular epidermis with a nonparakeratotic scale, especially pronounced at the follicle openings. In some places the suprapapillary plates were thin. Papillary bodies often contained dilated blood vessels associated with edema. There was a slight dilation of the blood vessels in the upper part of the corium, and these were surrounded with edema and round cells. There was some pigment in the corium. The collagen fibers showed a moderate edema.

DISCUSSION

DR. PAUL E. BECHET: I agree with the diagnosis of lichen spinulosus.

DR. HOWARD FOX: This eruption seems to be confined to groups of follicles, some of them showing tiny keratoses. One of the patches, which shows no redness, could be called circumscribed keratosis pilaris. It is not the picture of lichen spinulosus. This might represent an avitaminosis, and, if other remedies fail, one might well try large doses of vitamin A.

DR. GEORGE MILLER MACKEE: I do not think this condition is lichen spinulosus. I think the diagnosis of eczema is probably correct. It is eczema with one or two patches on the trunk that happen to have an unusual follicular involvement. The patch on the leg, however, is not follicular and is lichenified and looks like circumscribed neurodermatitis. It might possibly be due to a fungus. It might also be due to a vitamin deficiency, as has been suggested. Roentgen ray treatment might give a satisfactory result; if not, one might give 200,000 U. S. P. units of vitamin A daily.

DR. EUGENE F. TRAUB: When I first saw this patient I too thought of the possibility of a fungous infection as playing some role in this condition. He has

something between the toes that suggests the possibility of a fungous infection, but both cultures and smears of material from these parts have given negative results. While that does not exclude it definitely, there is no positive evidence that the condition in any way is a fungous infection. The patches on the back have never, since I have seen the patient, looked like an ordinary eczema, although the section taken from the back seemed histologically to conform with the diagnosis of eczema, according to Dr. Barthel. It might be a localized keratosis pilaris, but the condition suggested most strongly is lichen spinulosus. The patient has had no roentgen ray treatment to date, as he has been irregular in his attendance at the clinic. He has been attending for about a year but has never followed through with anything conscientiously.

CLEVELAND DERMATOLOGICAL SOCIETY

C. G. LaRocco, M.D., *President*

J. E. Rauschkolb, *Secretary*

James R. Driver, M.D., *Reporter*

Oct. 30, 1941

A Case for Diagnosis (Sarcoidosis? Tuberculoid Leprosy?). Presented by Dr. Donald MacVicar.

F. W., a Negress aged 40, presented from the department of dermatology and syphilology, Lakeside Hospital, was admitted to the hospital in June 1941, complaining of lumps in her skin. She was born in Alabama and had lived there for nineteen years, at the end of which time she moved to Cleveland. One year previous to admission she noted swelling and tenderness of the finger joints followed shortly by the appearance of numerous swellings in the skin of the entire body.

Examination reveals a sharply defined eruption, most extensive on the trunk, arms and thighs. There are also a few lesions on the cheeks, nose and eyebrows. The left ala of the nose reveals a castor bean–sized nodule extending outward and downward. The lesions vary in size from that of a nickel to ovoid tumors as large as a hen's egg. They are rather firm and the same color as the rest of the skin or slightly lighter. There is no evident enlargement of the veins. No areas of anesthesia are to be found on the body. The hands show a swelling of the phalangeal joints and on palpation have a rubbery or cystic consistency. The lymph nodes are generally discrete and not particularly enlarged.

The hemogram was normal except for a moderate hypochromic anemia. The Kline and Wassermann reactions of the blood were strongly positive. A complement fixation test of the blood with spirochetal antigen performed by Dr. Eagle gave a strongly positive reaction. The plasma proteins amounted to 8.15 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 0.92. The blood calcium, phosphorus and phosphatase values were normal. Roentgenograms of the skeleton and chest revealed small punched-out areas in the phalanges of the feet and hands and linear areas of infiltration in the lower half of the pulmonary fields with an enlarged lymph node in the superior right mediastinum. Stained smears of material taken from the nose and examination of tissue removed from several lesions showed no acid-fast organisms. The spinal fluid was normal. Intracutaneous tuberculin tests with old tuberculin elicited positive reactions in a dilution of 1 : 1,000.

Histologic examination of tissue removed from several lesions revealed nests and sheets of epithelioid cells surrounded by connective tissue and lymphocytes.

No necrosis was seen. The tonsils were removed, and histologic examination revealed considerable hyperplasia of the endothelial reticular cells.

Antisyphilitic treatment continued for several months resulted in only a slight improvement.

DISCUSSION

DR. H. N. COLE: I should like to ask the privilege of having Dr. Horace K. Giffen discuss this patient. He has lived in Egypt for many years and is an authority on leprosy.

Fig. 1.—A case for diagnosis (sarcoidosis? tuberculoid leprosy?).

DR. HORACE K. GIFFEN (by invitation): I have observed many cases of leprosy about which there was no question as well as a good many cases of a clinical picture similar to so-called Boeck's sarcoid. Now as to whether these two diseases are one and the same thing or whether my diagnosis has been wrong may be questioned. However, all over the world such conditions are found among leprosy contacts. Where leprosy is prevalent these sarcoid lesions are also found, often in persons known to be contacts. Histologically they cannot, by any known means, be differentiated from Boeck's sarcoid. Professor A. A. Stein in Russia has

written an article (Tuberculoid Changes in Leprosy, *Internat. J. Leprosy* **8**:41-53 [Jan.-March] 1940) in which he stated that the lesions do not differ from lupus and Boeck's sarcoid. Dr. Reenstierna published an article (*Acta med. Scandinav.* **103**:118-122, 1940) in which he made two statements which I think are correctly interpreted. The first is that the fact that one considers these lesions capable of being, among others, of leprous origin is not surprising when one encounters cutaneous lesions of leprosy with microscopic characters which cannot be distinguished from those seen in sarcoid. His second statement is: "Boeck himself has given an example, frequently cited, of the truth of this observation, in a case in which histologically tuberculoid leprosy of the skin was diagnosed."

Certainly, in my experience, which is limited, this type of clinical and pathologic picture is strikingly characteristic of conditions seen commonly among lepers. Persons with that form of leprosy are bacteriologically normal except when in a reactive state. The osseous changes in the case presented today are said to be characteristic of Boeck's sarcoid. I know of no studies published on the osseous changes of the tuberculoid type of leprosy. Histologically they appear identical. Sections from this case and from 2 cases of well established leprosy, 1 from the Virgin Islands and 1 from Egypt, with the labels covered, were given to Dr. H. T. Karsner, professor of pathology at the medical school, and he could not tell which was Boeck's sarcoid and which was leprosy. I am sure that any one who has had any experience with leprosy would have the same difficulty. Dr. Saunders, who has been making a survey for the American Leprosy Foundation and has been seeing leprosy all over the world, is positive that this case is one of tuberculoid leprosy. I feel the same way, even granting that the roentgen ray observations may conform to those of the so-called Boeck's sarcoid. This clinical picture is distinctly characteristic of that seen among lepers. Boeck's sarcoid is said to come and go periodically and to increase and decrease, and this is true of this form of leprosy. In some cases there is complete remission, while in others the condition recurs and becomes active again.

As far as I am concerned, in spite of the prevailing opinion, the condition in this case is a tuberculoid form of leprosy.

DR. R. E. BARNEY: It is my impression that all patients with tuberculoid leprosy are bacteriologically normal.

DR. HORACE K. GIFFEN (by invitation): Yes, except when the condition is in a distinctly reactive stage. It can be diagnosed histologically and clinically and yet be bacteriologically normal.

DR. H. N. COLE: We are much indebted to Dr. Giffen for coming here and discussing this case.

Here is a Negress from northwestern Georgia. She has never been out of that part of the country except to come to Cleveland. She has cutaneous changes consisting of a rather doughy type of nodules and tumors generally distributed over the body and on the lobes of the ears. She also has an unusual nodular process attached to the left naris. There are no ulcers on the mucous membranes. She has osseous changes of the digits which are characteristic of Schaumann's disease (lymphogranulomatosis benigna) or Boeck's sarcoid. This disease has been described by Schaumann, and more has been done to clarify its picture by him than anybody else. She also has changes in the lungs. The roentgenograms of the lungs are characteristic of those seen in Boeck's sarcoid, the fanlike areas of shadow radiating out from either side of the hilus. Moreover, she has an anergy down to 1:1,000, which is unusual for a Negro. She does have a serologic diagnosis of syphilis. It was suggested this was in favor of a diagnosis of leprosy. One must remember that between 30 and 50 per cent of Negroes from that part of the country have syphilis; so that does not mean much.

Dr. McCoy, consultant for the United States Public Health Service, told me that it is with this type of tuberculoid leprosy that there is the greatest difficulty in diagnosis and especially in differentiating from Boeck's sarcoid. As far as he

knew, there had not been many cases of leprosy from Alabama within the last twenty-five to thirty years, and he has been hunting up cases all over the country.

This is an extremely interesting case from the standpoint of differential diagnosis, and it should be carefully followed.

DR. HORACE K. GIFFEN (by invitation): This patient told me that she had worked as a cook in New Orleans and other places along the Gulf coast. Dr. McCoy certainly will tell you that there is plenty of leprosy in that region.

DR. B. F. BARNEY: This woman may have syphilis, but recently Dr. Kahn was working on a verification test by which he may be able to exclude such a possibility. It might be advisable to send blood to Dr. Kahn and determine whether the reaction is of the biologic or of the syphilitic type.

DR. G. W. BINKLEY: In the investigations carried out on this patient it was believed that Kahn's verification test would not be of help, but that Eagle's flocculation test, using spirochetal antigen in place of the usual beef heart antigen, would be of more importance. This test was performed, and the serum did not behave like leprosy serum. It reacted positively, as in cases of syphilis, in other words, it showed a reaction as a syphilitic serum rather than as a leprosy serum.

I believe that cases of this type in this part of the country should be regarded as instances of Schaumann's disease if the condition does not progress to bacteriologically positive leprosy. In all of the cases of sarcoid that have been reported from Scandinavia and France, the condition has remained sarcoid and has not transmuted into leprosy.

DR. R. E. BARNEY: There was no involvement of the supraorbital ridges, and I should like to ask Dr. Giffen if that is the rule in tuberculid leprosy.

DR. HORACE K. GIFFEN (by invitation): It is my opinion that lesions occur on almost any part of the skin in relatively symmetric positions. I do not think that the site is either for or against the diagnosis.

A Case for Diagnosis (Reinfection in Congenital Syphilis?). Presented by DR. GEORGE M. STROUD.

F. H., a white man aged 36, presented from the department of dermatology and syphilology, Lakeside Hospital, was admitted to the hospital on Sept. 30, 1941 because of a penile sore of two months' duration. In 1925 he had had bilateral interstitial keratitis and a positive Wassermann reaction of the blood and of the spinal fluid. He received fairly regular treatment, consisting of fourteen injections of arsphenamine and one hundred and eleven intramuscular injections of a bismuth compound. He also had taken potassium iodide on and off for two years. In 1928 the Wassermann reaction of the blood became negative, and in 1930 that of the spinal fluid became negative. Except for a few weakly positive Kline reactions, many subsequent serologic tests as late as 1939 gave negative results. Repeated periodic check-ups, the last in 1939, showed no evidence of syphilis excepting healed interstitial keratitis. Two months before entry he noted a blister on the inner surface of the prepuce. It ruptured, and he extracted what he described as a rose thorn. This was followed by a slightly painful ulcer.

Physical examination reveals a moderately tender indurated punched-out ulcer with a dirty sloughing base about 1 cm. in diameter located on the dorsal surface of the reflected foreskin. The inguinal lymph nodes are moderately enlarged, discrete and painless.

Repeated dark field examinations of material from the lesion and from an inguinal lymph node did not show Spirochaeta pallida. Repeated Frei and Ito-Reenstierna tests gave negative results. A tuberculin test with a dilution of 1 : 1,000 elicited a slightly positive reaction. Aerobic and anaerobic cultures of material from the penile lesion showed only Staphylococcus aureus. During his stay of approximately one month in the hospital serologic tests were performed twice

weekly. The Wassermann reactions have been consistently negative. The Kline diagnostic tests have resulted in doubtful reactions, while the Kline exclusion tests have shown a progressive positivity. Agglutination with Bacillus tularensis gave a negative result.

Histologic examination of a section taken from the ulcer showed slight acanthosis. There was a fairly diffuse infiltrate in the subepithelial connective tissue consisting predominantly of neutrophils and in addition eosinophils, lymphocytes and large histiocytes. There was proliferation of fibroblasts, and the tissue was moderately well vascularized. Acid-fast and Giemsa stains failed to reveal a specific organism.

Because of the clinical appearance suggestive of chancroid, sulfathiazole (2-[para-aminobenzenesulfonamido]-thiazole) was given in doses ranging from 6 to 2.5 Gm. daily. On the ninth day fever and a generalized erythema developed. Administration of the drug was discontinued, and these symptoms subsided after forty-eight hours. Ten days later sulfathiazole powder was applied to the lesion, and after twelve hours there were edema and inflammation of the lesion and the penis, together with a recurrence of fever and generalized erythema. These symptoms subsided in about twenty-four hours.

Fig. 2.—A case for diagnosis (reinfection in congenital syphilis).

In appearance the lesion was now suggestive of phagedena. Zinc peroxide dressings have been applied for the past five days without any noticeable improvement.

DISCUSSION

DR. I. L. SCHONBERG: I should like to suggest a diagnosis of phagedena.

DR. H. A. HAYNES JR., Akron, Ohio: Have anaerobic cultures for hemolytic streptococci been made?

DR. H. N. COLE: I do not think that syphilis has been ruled out yet. I still think this is a possible diagnosis. It is true that the patient has had congenital syphilis, but that does not necessarily mean that he has not contracted an infection. Sufficient time has not elapsed to rule out this possibility. Yesterday, Dr. Johnson suggested the practicability of starting antisyphilitic treatment. I would be interested to hear what some of the members think of this proposal. Should the patient be followed and serologic tests made once a week, or should he be given treatment in an effort to prove or disprove the presence of syphilis?

DR. H. H. JOHNSON: The only reason that I made the proposal was that the lesion has been carefully investigated without a diagnosis being made. The patient has been in the hospital for a month, and the lesion is over three months old. As far as an anaerobic streptococcic infection is concerned, this patient has been

given sulfathiazole for a fairly long time without any improvement. In fact, the lesion became worse under that therapy. For lack of a satisfactory diagnosis and knowing that he had had syphilis, I thought it might be worth while to give him a therapeutic trial. If the therapy was not effectual the treatment could be terminated.

DR. H. N. COLE: All the members have seen patients with genital lesions resembling this one from infections resulting from unusual practices, and that is the method by which this man has contracted his. Usually Vincent's spirochetes are found, but they were not in this case.

DR. J. R. DRIVER: In the history I noted that dermatitis medicamentosa and fever followed the administration of what I believe are too large doses of sulfathiazole. It has been established that in the treatment of chancroid doses of approximately 2 Gm. per day are effective. Doses of approximately 6 Gm. per day are dangerous and frequently result in serious reactions. Evidence of extreme sensitization resulting from this reaction is shown by a recurrence of the symptoms following the local application of the drug ten days later.

NOTE.—The lesion healed promptly after five intravenous injections of mapharsen.

A Case for Diagnosis (Scleroderma? Lymphangioma? Nevus?). Presented by DR. GEORGE H. CURTIS and DR. E. W. NETHERTON.

H. M., a Jewess aged 13, noticed a slightly pruritic and elevated spot on her back about the size of a quarter in September or October 1940. Since initial slight itching there have been no subjective symptoms. The lesion has been progressively enlarging to its present size. She has taken ex-lax occasionally as a cathartic.

General physical examination showed no abnormalities. A roentgenogram of the chest showed fibrosis in the region of the hili.

The lesion measures 6 by 8 inches (15 by 20 cm.) and is located just below the left scapula. The border is indefinite and the shape irregular. The central portion appears puffed and edematous, but there is no pitting on pressure. The surface is wavelike, and this appearance becomes more distinct toward the periphery, with the crests having a retiform arrangement. The color is normal except for the presence of numerous pinhead-sized discrete keratotic spots most of which are perifollicular and distributed on the crests of the wavelike elevations. There is no gross follicular plugging. The hemogram and the urine were normal. Tuberculin tests with prepared protein derivative no. 1 and no. 2 gave negative results. The basal metabolic rate was — 14 per cent.

The most striking feature of the pathologic section taken from the central edematous part of the lesion was edema extending from the upper part of the corium down to beyond the coil glands.

There was a mild follicular hyperkeratosis and thickening of the horny layer. The epidermis otherwise was normal.

The papillae and the upper portion of the corium showed some edema, which was mainly perivascular and in which there was a small number of round cells. At one place in the upper portion of the corium, near a hair follicle, there was a small localized area of edema, with mild round cell infiltration that had destroyed the architecture of the collagen and elastic fibers.

DISCUSSION

DR. H. N. COLE: I think the lesion closely resembles the doughy type of edema seen in connection with localized types of myxedema. The histologic picture would also go with it. The basal metabolic rate was — 14 per cent, and I think more tests should be performed in order to check on this. Also stains for mucin should be made.

DR. R. E. BARNEY: I suggest the possibility of an edematous stage of scleroderma. Sections should be stained for elastic tissue.

DR. J. E. FISHER: I saw this patient about six months ago. The condition was somewhat more edematous but perhaps not so extensive. I have no diagnosis to offer, but I believe a localized type of myxedema, as Dr. Cole has suggested, should be considered.

DR. E. W. NETHERTON: Dr. Cole's suggestion regarding staining to determine whether the area in the upper portion of the corium, which has been interpreted as edema, is mucin is a pertinent one.

In regard to this condition's being a localized myxedema, I should like to point out that localized myxedema is seen almost exclusively in cases of recurrent hyperthyroidism and that the lesions are located in the tibial region. However, cutaneous lesions may occur elsewhere in any case of localized myxedema in which the anterior surfaces of the legs are involved. This patient has never had hyperthyroidism.

The most striking thing about the histologic structure in this case is that there are numerous follicular plugs which are not accompanied by inflammatory reaction in the corium. It is difficult to explain this follicular change, particularly since clinically there is little evidence of plugging of the follicles.

We have thought of the following possibilities in this case: lymphangioma, scleroderma and a nevoid change of some kind. The histologic examination rules out the possibility of a lymphangioma; however, the picture might fit into the possibility of scleroderma. There is no atrophy or hyperpigmentation, which is usually seen in scleroderma. So far, we have been unable to classify this case.

DR. HORACE K. GIFFEN (by invitation): If another specimen for biopsy is taken, I suggest that it be taken from an uninvolved area for a control. Otherwise, the histologic picture may be easily misleading.

A Case for Diagnosis (Pustular Psoriasis? Acrodermatitis Continua [Hallopeau]? Result of Sulfathiazole Therapy?). Presented by DR. GEORGE H. CURTIS and DR. E. W. NETHERTON.

J. T. Z., a woman aged 26, was presented before this society on March 27, 1941 (ARCH. DERMAT. & SYPH. **45**:434 [Feb.] 1942), at which time she presented chronic pustular lesions of the hands and feet. She is presented to show the effect of treatment.

From February to June 1941 the patient received seventeen intramuscular injections of 0.2 Gm. of bismarsen. The treatment was ineffective. From June to September 8 no treatment was given, and the disease remained essentially the same.

On September 8 and every day for two weeks the patient was given 2 Gm. of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), and within two days the lesions began to disappear. In two weeks healing was complete, and to date, October 30, there has been no recurrence.

DISCUSSION

DR. GEORGE H. CURTIS: When we presented this case before the society last March, we were more inclined to think that the condition was acrodermatitis continua (Hallopeau). On the possibility that it might be lupus erythematosus the patient was given a great deal of treatment with bismarsen. The course of the dermatitis was not affected either during or following this treatment. Within two days after sulfathiazole therapy was instituted the lesions began to clear up, and in two weeks they were completely well.

DR. H. J. PARKHURST, Toledo, Ohio: I noted pustular psoriasis had been considered in the differential diagnosis. The patient gave no history of it and showed no lesions of psoriasis either on the skin or on the nails. I favor a diagnosis of acrodermatitis continua. This disease may fall into either one of two groups: those due to focal infection and those occurring on a neurogenous basis. The response to sulfathiazole would seem to indicate that the condition in this case was in the former group.

Pemphigus Foliaceus and Avitaminosis. Presented by DR. DONALD MACVICAR.

F. P., a 55 year old white woman, presented from the department of dermatology and syphilology, Lakeside Hospital, was admitted to the hospital complaining of an eruption of four years' duration. Her history revealed that eleven years ago she had had a left nephrectomy performed, supposedly for tuberculosis of the kidney. Three years ago she was found to have diabetes. Four years ago she first noticed a slightly itchy red eruption under the left breast, which gradually spread to involve almost the entire body and has persisted with remissions and exacerbations until the present time. For several months she has noticed anorexia, lassitude and spells of nausea and vomiting.

She is pale and weak and appears chronically ill. On the trunk, extremities and face are many large reddish brown areas covered with thin, greasy, easily removed crusts. Beneath the crusts the surface presents a red weeping surface. The borders of these areas are sharply defined and often serpiginous. A few vesicles and small bullae appear in some areas. The eruption is most prominent in the axillas, groins and intergluteal region and beneath the breasts. The mucous membrane of the mouth presents an angry red color with perlèche-like lesions at the labial commissures. There are associated blepharitis and conjunctivitis. The hair is coarse and thin, and the scalp appears white and shiny. Nikolsky's sign was present.

The hemogram showed a rather severe anemia. The leukocyte and differential counts were normal. Glycosuria and hyperglycemia were present. The protein content of the plasma was 6.09 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 0.79. The ascorbic acid content of the plasma was 0.54 mg. per hundred cubic centimeters. Complete chemical examination of the blood showed that it was otherwise normal. Biophotometry showed poor dark adaptation.

Histologic examination showed intraepidermal vesicles filled with polymorphonuclear leukocytes. Throughout the corium there were focal collections of lymphocytes, polymorphonuclear leukocytes and plasma cells.

DISCUSSION

DR. I. L. SCHONBERG: I saw the patient about a year ago, at which time she presented erythematous lesions on the face, some in acute form. Under the breasts there was an erythematous macerated eruption accompanied by exudation. Examination of the patient's mouth revealed a smooth raw beefy tongue, suggesting avitaminosis. At that time I considered several diagnoses but could reach no definite conclusion. A smear of material from one of the sections showed Monilia, which, of course, could have been a secondary invader. I prescribed a high vitamin diet, and she showed slight improvement. When small doses of potassium iodide were administered, there was an exacerbation of all symptoms, which I interpreted as favoring a diagnosis of dermatitis herpetiformis. Local treatment consisted of application of gentian violet and potassium permanganate compresses. Several weeks later her face cleared up, but the eruption never completely disappeared. From time to time she had an acute exacerbation.

DR. J. R. DRIVER: This patient has made a remarkable improvement in the last ten days or two weeks. Local therapy consisted of application of mild bismuth tribromphenate and tar ointment. She has received full doses of vitamin B complex and other vitamins. The eruption is entering a stage of at least partial remission. The clinical appearance and the chronic course of the disease characterized by remissions and exacerbations are typical of pemphigus foliaceus.

DR. BENJAMIN LEVINE: I saw this patient about three years ago, and at that time the eruption was generalized. There was considerable exfoliation, and there were also lesions in the mouth. The tongue was beefy red, as described by Dr. Schonberg. At one stage she had a temperature of 105 F. She was given large doses of sulfanilamide, and the eruption entirely disappeared. She was also

given a high vitamin diet and intramuscular injections of crude liver extract, to which she seemed to respond at that particular time. I favored a diagnosis of dermatitis exfoliativa at that time, but now I agree with the diagnosis of pemphigus foliaceus.

DR. E. W. NETHERTON: She has an interesting eruption of the scalp, which I believe is folliculitis decalvans, although the follicular plugging and atrophy present suggest lupus erythematosus. Are these changes coincidental, or are they considered by the presenter as associated with the pemphigus?

DR. J. E. FISHER: The patient stated that the eruption on the scalp had been present since childhood. Her mother put a strong medication on her scalp, and she attributed the loss of hair to that.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

LOUIS TULIPAN, M.D., *Chairman*

T. J. RIORDAN, M.D., *Secretary*

Nov. 5, 1941

Generalized Pityriasis Rosea, with Palmar, Plantar and Genital Lesions.
Presented by DR. WILLIAM LEIFER.

F. R., a white man aged 47, married, a salesman, first appeared at the Lower West Side Social Hygiene Clinic of the Department of Health on Oct. 28, 1941. He stated that he had had a penile sore in 1920 and that a diagnosis of syphilis was made in the United States Army. He received both intravenous and intramuscular injections for one year. Repeated serologic tests of the blood since then have given negative results, the last having been performed about four months ago.

On admission he complained of a nonitching eruption which had appeared more or less abruptly about one week previously. He stated that there had been no precedent penile or other lesion. There was no history of the ingestion of drugs.

The eruption involved the neck, trunk, arms, forearms, thighs and legs. Lesions were also present on the penis and scrotum, and a solitary lesion was seen on the left palm and another on the left sole. Two distinct types of lesions were present. One was a dark red firm papule without scales, and the other was a larger superficial pink macule. The papular lesions were most evident on the trunk and upper extremities and in the axillary regions. The palmar and plantar lesions were distinctly papular. The lesions on the genitals were macular.

When the patient was seen four days later the macular lesions on the trunk had become ovate, with the long axis in the lines of cleavage, and slight scaling was present.

No lymphadenopathy is present, and the accessible mucous membranes are clear.

Repeated dark field examinations of material from one of the papular lesions gave negative results. The Wassermann reaction of the blood was negative on October 28.

DISCUSSION

DR. LOUIS CHARGIN: It is exceedingly difficult to diagnose the condition at this stage of the eruption. One has to take into consideration syphilis, pityriasis rosea and possibly parapsoriasis. The eruption is somewhat too red for syphilis, though in many respects the lesions on the trunk—macules and papules—together with the distribution, do suggest syphilis. However, the serologic reports and

dark field examinations are strongly against syphilis. Moreover, the patient states that he had a syphilitic infection years ago. Parapsoriasis of the acute variety is suggested by a few lesions which appear to be varicelliform. Also, many of the other lesions, particularly on the arms, suggest parapsoriasis. If one were to look at the back alone, pityriasis rosea would seem the most probable diagnosis, but one can hardly accept this diagnosis for the lesions on the forearm and scrotum. I do not recall having seen lesions of pityriasis rosea on the scrotum, though I have seen them on the palms, as in this case. I favor a diagnosis of parapsoriasis.

DR. FRED WISE: Dr. Chargin has mentioned the points of differential diagnosis. In addition, it is noteworthy that the papule of syphilis is susceptible to a sensation of pain on pressure with a blunt probe, while that of parapsoriasis is not. While the arrangement of lesions along the lines of cleavage on the back is most often seen in pityriasis rosea, I too favor a diagnosis of parapsoriasis.

DR. CHARLES WOLF: I suggest a diagnosis of lichen planus. A biopsy should be performed.

DR. LOUIS TULIPAN: I believe the patient had a lesion on the hard palate, which certainly would not fit in with a diagnosis of pityriasis rosea. It is such a rarity in that condition that I think it would probably rule out that diagnosis.

DR. WILLIAM LEIFER: In a comprehensive survey of pityriasis rosea, the late H. D. Niles and M. M. Klumpp (ARCH. DERMAT. & SYPH. **41**:265 [Feb.] 1940) referred to several cases in which it had been reported that there were typical lesions of pityriasis on the genitals. There are many cases in the literature in which there are lesions on the palms and soles and also on the tongue and palate. The unusual distribution of lesions in this case does not rule out the diagnosis of pityriasis rosea.

Keratosis Follicularis (Darier's Disease) Treated with Vitamin A.
Presented by DR. SAMUEL M. PECK.

G. H., a white man aged 27, was presented before this society about three years ago with the same condition, which was first noted sixteen or seventeen years ago. The family history is negative as far as a similar eruption is concerned.

The patient was first seen by me on Jan. 9, 1941. At that time the palms presented yellowish hyperkeratotic lesions, and on the backs of the hands, especially the fingers, the skin was greatly hyperkeratotic, especially over the joints. The forehead and sides of the nose showed scattered hyperkeratotic papules. The scalp was relatively free of lesions. Behind the ears, on the back of the neck and on the trunk, especially along the sides extending into the axillas, there were numerous single and grouped typical hyperkeratotic papules, usually around hair follicles. The arms, especially the flexor surfaces, as well as the knees, also showed patches of hyperkeratosis which were essentially grouped follicular hyperkeratotic lesions. Discrete follicular papules were seen on the inner surfaces of the thighs and in the inguinal regions. The mucous membranes were unaffected.

Blood was taken on January 15 and showed vitamin A, 66 U. S. P. units, and carotene, 163 micrograms. He was given 200,000 U. S. P. units of vitamin A daily by mouth and 100,000 U. S. P. units intramuscularly. Blood was again taken on March 3 and showed vitamin A, 36 U. S. P. units, and carotene, 62 micrograms. When the intramuscular injections were stopped and vitamin A was given by mouth alone, the blood level of the vitamin A rose sharply, so that on March 16, 1941 he showed 93 U. S. P. units of vitamin A and 61 micrograms of carotene. He has continued to take approximately 200,000 U. S. P. units daily since that time. His last blood examination, on October 21, when he had been taking 250,000 U. S. P. units for about a month, showed vitamin A, 144 U. S. P. units, and carotene, 83 micrograms.

Studies of dark adaptation were made by Dr. Selig Hecht, of Columbia University. The first was performed on January 8, before vitamin A was given, and it was found that he had a threshold definitely higher than normal. The examination was repeated on February 21, after he had been taking 200,000 U. S. P. units a day, and there was considerable improvement in his vision, so that cone vision was just on the margin of normal, while his rod vision was not quite normal.

A biopsy of material from one of the lesions on the hand on January 22 showed the characteristic picture of keratosis follicularis with many *corps ronds* and grains.

Since the beginning of the study the patient has shown a decided involution of the lesions. There is still evidence of the disease on his hands, as well as a few scattered papules behind the ears. Around the mouth and on the eyelids there is a superficial scaling dermatitis. During the summer nearly all of the areas which seemed to have responded well to vitamin A therapy showed some recurrence of redness and scaling. This was especially noticeable around the eyes and in the axillas. The lesions were more acute and were somewhat reminiscent of the vesicular type of keratosis follicularis. This occurred in spite of the continuation of administration of vitamin A by mouth. There was prompt involution of these symptoms with the onset of cool weather. This recurrence of rather acute keratosis follicularis in areas of profuse sweating has been noted in other cases of this disease during hot weather.

DISCUSSION

Dr. Louis Chargin: The patient was presented, first, to show the beneficial effect of vitamin A; this is especially true in cases of mild keratosis follicularis. Secondly, when the vitamin was given by injection there was, for some unknown reason, a definite decrease of the vitamin content of the blood. On the other hand, when it was given by mouth there was a gradual increase of vitamin in the blood. This behavior of the vitamin has been observed in several cases. A third point worth mentioning is that in spite of the fact that this patient has continued taking the vitamin without a stop in doses of 200,000 U. S. P. units daily, the disease became aggravated during the summer months. That seems to be a common experience in cases of this disease.

Dr. Fred Wise: When I first learned of the success of Dr. Peck's treatment of keratosis follicularis with large doses of vitamin A, I was very skeptical. I had been imbued with the idea that the entire group of hereditary, familial, nevoid eruptions, such as keratosis follicularis and Recklinghausen's diseases and ichthyosis, were not responsive to internal remedies. I now realize the fact that keratosis follicularis can be considerably influenced by vitamin A medication and that Dr. Peck deserves credit for his work in this field. The eruption in the patient shows great improvement. In the treatment of follicular and perifollicular hyperkeratoses, in keratosis pilaris and spinulosa I have been disappointed with vitamin A therapy in that large doses were ineffectual in several male patients under my personal observation.

Dr. E. William Abramowitz: Some believe that a vitamin A deficiency exists in many diseases of the keratotic type—anything from keratosis pilaris to ichthyosis. I have a patient now, a young woman, with keratosis follicularis, who has lesions in the mouth. She has been taking 150,000 to 200,000 U. S .P. units of vitamin A daily by mouth for the past six months, with a remarkable improvement in her condition. There have been no ill effects. It would be interesting to examine patients with other cutaneous diseases or normal persons to determine their ability to convert the provitamin into vitamin A and also to determine the vitamin A content of the blood.

Dr. Charles S. Miller: I have used vitamin A in keratosis pilaris and also in keratosis follicularis, and my experience has been the same as that of Dr. Wise. There was not much response in keratosis pilaris, but it should be remembered

that keratosis pilaris in no way resembles keratosis follicularis histologically. In keratosis pilaris there is a nonspecific type of inflammatory reaction about the follicles, while in the other disease there is a dyskeratosis of some epidermal cells.

DR. CHARLES LERNER: I think a possible explanation for the unsuccessful results of Drs. Wise and Miller in treating keratosis pilaris and ichthyosis with vitamin A is that both these conditions are atavisms, or reversions to a primitive type, whereas keratosis follicularis, in my opinion, is acquired. It is possible that the endocrine system is involved in all of them, that is, embryologically and structurally in keratosis pilaris and ichthyosis and only functionally in keratosis follicularis. The definite linking up of endocrines with vitamins is still to be accomplished and remains for future biochemistry to clarify. In my opinion, the much greater improvement of the lesions on the body of Dr. Peck's patient, as compared with that on the hands and soles, is probably due to the fact that the lesions in the latter places are located in areas of terminal circulation, and all lesions generally clear less rapidly in such areas. It would be interesting to determine quantitatively the amounts of vitamin A in sections of the skin taken from the body and from the palms and soles.

DR. CHARLES WOLF: The remark that there is no danger in giving immense doses of vitamin A over long periods is not entirely in keeping with facts. It is known that hypercarotinemia may occur from excessive amounts ingested as carrots and green vegetables. I believe I saw a chamois-colored xanthomatous discoloration of the skin in this patient. Even cod liver oil has been known to cause untoward reactions, such as eczema and urticaria.

DR. JESSE A. TOLMACH: In regard to vitamin A, except for those cases in which a history of insufficient feeding and/or hemaralopia is obtained, the indications for its use are, in the main, empiric. The accuracy of the biophotometer is a matter of dispute, and, similarly, chemical analysis of the blood for vitamin A is not yet sufficiently standardized for reliable interpretation. Until laboratory methods for accurately determining deficiencies in vitamin A are perfected, investigations in this field will have to be continued on an empiric basis.

DR. HERMAN GOODMAN: It would be interesting to know if, after three months of treatment with tremendous doses of vitamin A, there were an exacerbation when it was stopped. Then one would have to decide whether the part of the eruption that responded to vitamin A was the part that was due to deficiency, while the part that remained was the hyperkeratosis due to keratosis follicularis. The specificity of vitamins on gland structure must also be considered.

DR. E. WILLIAM ABRAMOWITZ: In reply to Dr. Wolf, one may get carotinemia with excessive doses of carotene but not with large doses of vitamin A.

DR. MAURICE J. COSTELLO: It is interesting to note in this case that the patient's night blindness gradually disappeared as his cutaneous eruption improved. He told me that formerly he had difficulty in driving a car at night.

DR. DAVID BLOOM: It is a mistaken conception that hereditary disease is not amenable to treatment. The visible cutaneous manifestation of a hereditary defect should not be conceived as the direct immediate result of a change in the germ plasm. It should rather be thought of as depending indirectly on one or more factors which are the primary expressions of an abnormal gene, producing the disease manifestation. In the case of keratosis follicularis, one of the underlying factors producing the cutaneous manifestation seems to be, as Dr. Peck has shown, a disturbance in the vitamin A absorption. Treatment directed to this underlying factor will, as one should expect, influence beneficially the cutaneous disease.

DR. LOUIS CHARGIN: I think it is necessary to remember in this question of vitamin A and keratosis follicularis that treatment with vitamins is believed to be a sort of replacement therapy. These patients for some reason are unable to utilize the vitamin A in their food, and it is reasonable to expect that those with a mild type of keratosis follicularis particularly should respond to the administration of

vitamin A. How it acts is not known, but one can speak of an effect. In reply to Dr. Goodman, in this case the treatment has been stopped and the disease has become worse and then improved again when vitamin A therapy was resumed. The improvement takes place only to a certain point—the lesions do not disappear completely—but there is no question about the regression. Dr. Peck and I now have some 10 or 12 such patients under our care, and while Dr. Peck, I am sure, does not claim cures in any, there certainly has been much improvement. I do not think any harm results from large doses of vitamin A. I should like to stress the point that this is a replacement therapy.

Epidermodysplasia Verruciformis (Lewandowsky and Lutz). Presented by DR. HENRY SILVER.

H. M., a woman aged 26, a deaf-mute, was previously presented before the Bronx Dermatological Society in February 1941 (ARCH. DERMAT. & SYPH. **44**: 720 [Oct.] 1941).

Several lesions from the fingers and face removed for histologic study showed typical verruca vulgaris. A section from a lesion clinically diagnosed as seborrheic keratosis showed decided downgrowth of the epidermis with the formation of horn pearls. This ectodermal hyperplasia indicates beginning carcinomatous change.

A lesion on the back of the right index finger was treated with roentgen rays (total dose, 1,100 r). The lesion has flattened considerably. Recently one plaque on the palm was also subjected to roentgen ray treatment (total dose to date, 450 r). There is no change in this lesion.

DISCUSSION

DR. FRED WISE: The eruption bears some resemblance to the original description of epidermodysplasia verruciformis, while the histologic picture does not appear to conform with that in other cases. In other cases the epidermis showed a basket-weave-like formation of clear cells with flattened eccentric nuclei. The eruption in this patient shows some points of similarity to acrokeratosis verruciformis clinically.

DR. CHARLES WOLF: I cannot blame Dr. Wise for being disinclined to concur in the diagnosis. As a matter of fact, Hoffman and Kogoj held the opinion that epidermodysplasia verruciformis was a manifestation of verruca vulgaris. However, there are reasons for believing that it may be a disease sui generis: First, it has been observed that some of the lesions go on to malignant degeneration, and secondly, there is a typical histologic structure. The case presented by Dr. Silver fills these dicta to a certain degree. There is a combination of lesions found in verruca vulgaris and epidermodysplasia verruciformis, so that one who is influenced by the presence of the verruca vulgaris type naturally will not be too ready to accept the diagnosis of the unusual condition.

DR. FRED WISE: I want to make a little correction with respect to Dr. Wolf's statement, which is likely to be confusing. He implied that the diagnosis based on the finding of ordinary warts would not be likely to lead to identification of epidermodysplasia verruciformis, and this is true. But it is necessary to examine histologically not the ordinary warts which are found mostly on the hands but the small scaling nodules which preponderate in nearly all eruptions thus far reported. The histologic character of the latter is characteristic.

DR. HENRY SILVER: I must agree with Dr. Wise that my case does not present all the features of epidermodysplasia verruciformis. There are, however, enough factors—clinical and histologic—to warrant a definite diagnosis of the disease. Epidermodysplasia verruciformis, as is known, is rare, and many years pass before a case comes under observation. The recorded cases show many variations, particularly in the clinical picture. Many show only such lesions as

were seen on the hands and legs of my patient and no other lesions, and yet they have been accepted as instances of epidermodysplasia verruciformis. My patient presents, in addition to the warty lesions with their characteristic translucency, lesions on the face resembling seborrheic warts, some of which show changes with a tendency toward malignancy. The histologic picture also supports the diagnosis because of the presence of the characteristic balloon cells and vacuoles described and reproduced in the article of Wise and Satenstein. Dr. Wolf's remarks are pertinent. I do not wish to settle the controversy as to whether the vacuolation and degeneration are specific for epidermodysplasia verruciformis. Kogoj and Hoffman expressed the opinion that vacuoles are observed in other keratotic anomalies. It is highly probable that epidermodysplasia verruciformis of Lewandowsky and Lutz, Hoffman's verrucosis generalisata and possibly Hopf's acrokeratosis verruciformis are clinical variations of the same entity.

Necrobiosis Lipoidica Diabeticorum in a Juvenile Diabetic Patient. Presented by DR. CHARLES S. MILLER.

C. G., a boy aged 8 years, is presented from the Queens General Hospital, Jamaica, N. Y., to which he was admitted on May 22, 1941, because of drowsiness and listlessness which had been present for one week. A diagnosis of diabetic acidosis was made, and subsequently sustained by laboratory examinations. The patient was discharged from the hospital on June 16 and was referred to the dermatologic clinic on September 23 because of several cutaneous lesions on the lower extremities.

On the dorsal surface of the right foot and on the outer aspect of the left ankle are two yellowish slightly raised patches. There is no scaling, no atrophy and no ulceration. The lesions are hard and firm to the touch.

Urinalysis showed a 3 plus reaction for sugar and the presence of acetone. The blood sugar content on May 26, 1941 was 187 mg. per hundred cubic centimeters and on June 5 132 mg.

A biopsy on October 23 revealed through the middle and lower parts of the cutis masses of collagen bundles which showed parenchymatous edema. About these masses was an inflammatory reaction composed of a few round cells and many histiocytes of the wandering connective tissue type. Some of the collagen bundles showed areas of vacuolation. The blood vessels throughout the cutis gave evidence of a vasculitis; the endothelial cells were swollen, and there were surrounding fluid and some perivascular infiltration. A Sudan stain revealed the presence of fat in the areas of vacuolation. The epidermis was essentially normal.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ: I accept the diagnosis. The interesting feature is the erythematous lesions that have appeared recently. These look like erythema centrifugum.

Pseudoleukemid. Lymphosarcoma Id. Dermatitis-Herpetiformis-Like Eruption in a Patient with Lymphosarcoma. Presented by DR. EUGENE T. BERNSTEIN.

M. H., a man aged 44, is presented from Beth David Hospital. One year ago he noticed edema of the ankle and of the cervical glands. A physician performed a biopsy of a cervical node and made a diagnosis of a possible leukemia. The histologic picture did not show a definite dyscrasia. In June of this year he noted swelling of the glands, and a rash developed with large blebs, vesicles, reddish areas and scaling. In February and July he was treated in Jamaica, N. Y., for this condition. A biopsy of a cervical node was interpreted as aleukemic lymphatic leukemia. In August he attended the Kings County Hospital, where it was reported that biopsy of a cervical node showed lymphosarcoma. All glands, and particularly those in the groin, were given radium therapy.

At present the patient appears to be not acutely ill and is strong, considering his long history. The heart and lungs are normal. The liver is enlarged and the spleen palpable. There are large glands in the axilla and in the groin.

The skin shows a polymorphous, macular, papular, vesicular eruption, with large pigmented spots on the lower extremities. There is a scattered pustular and papular eruption on the face. Urticaria-like lesions of papular character and some nondiscrete bluish red patches are seen on the trunk.

Histologic examination of a papulovesicular lesion revealed that throughout the entire cutis the vessels were dilated and filled with blood elements. There was a focal and diffuse cellular infiltrate composed of small round cells, some polymorphonuclear leukocytes and many wandering connective tissue cells. There was swelling of the vessel lining. The epidermis was secondarily acanthotic, and the center of the section was missing. Below this missing portion the cutis was necrotic and filled with polymorphonuclear leukocytes. The picture was considered to be consistent with a diagnosis of lymphosarcoma id.

DISCUSSION

DR. MAURICE J. COSTELLO: I think this patient has a leukemid because of the polymorphous appearance of the eruption and the nonspecific histologic picture. I believe that a generalized id of this type presages a general dissemination of the disease. I recently had a patient with lesions of this type in whom intensely pruritic nodules developed which later became hemorrhagic. Soon involvement of the liver and lungs developed.

MINNESOTA DERMATOLOGICAL SOCIETY

F. W. LYNCH, M.D., *President*

H. A. CUMMING, M.D., *Secretary*

St. Paul, Dec. 5, 1941

Multiple Pedunculated Fibromas of the Eyelids. Presented by DR. J. F. MADDEN, St. Paul.

J. S., a white man aged 59, stated that small tumors first appeared on the eyelids about 1930. A single lesion was noticed first, and new ones have been appearing at intervals since then. There are thirty or more pedunculated, pinhead–sized to millet seed–sized, soft, painless fibromas on the eyelids and surrounding skin. Some of the lesions are the color of normal skin, while others are hyperpigmented. There are also several flat, hyperpigmented macules on the face and other parts of the body. There are a few scattered fibromas on other parts of the face. The patient is highly emotional but seems to be of normal intelligence. The Wassermann reaction was negative.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: I accept the diagnosis as presented. I wish to state that I recently saw a patient who was suffering from acute urticaria and also had similar fibromas, each of which became edematous and took part in the urticarial process.

Dermatitis Papillaris Capillitii. Presented by DR. J. F. MADDEN, St. Paul.

H. U., a white man aged 27, stated that his mother first noticed a pustular eruption on the back of his neck when he was 1 year of age. There has been an eruption on the back of his neck as long as he can remember. He has had various other infections from time to time and now has marginal blepharitis.

The eruption is made up of coalescing keloids associated with folliculitis, abscess formation and a varying amount of hair loss. The Wassermann reaction was negative. The blood sugar content was 129 mg. per hundred cubic centimeters.

DISCUSSION

DR. L. A. BRUNSTING, Rochester: Examination of the neck reveals a pustular condition with keloidal scarring and an excessive oiliness of the skin with formation of comedos. In some ways this seems to be related to the presence of deep-seated acne elsewhere and perhaps may be a variant of dissecting cellulitis of the scalp and hydradenitis suppurativa of the axillas or of the inguinal folds, buttocks, perineum, scrotum and perianal region. Adequate treatment implies a proper balance of chemotherapy, roentgen therapy and destructive cautery. Many times excision and grafting in the early stage are the most effective treatment. In the early stage it is essential to pay particular attention to hygiene and to stimulating the general resistance by a program of rest, exposure to the sun and administration of an adequate diet supplemented by vitamin B complex.

DR. H. E. MICHELSON, Minneapolis: I think one should differentiate between two types of this disease. In older patients the lesions are usually dry and keloidal and do not have any sinus formation. In this type one may give about four times as much roentgen ray treatment as one would ordinarily think safe.

DR. W. C. POPP, Rochester: I am in accord with Dr. Michelson's suggestion that lesions of the chronic indurated type respond somewhat better to roentgen ray treatment than do active lesions in the form of sinuses. Lesions of this type will tolerate considerable repetition of treatment with no evident ill effect except epilation, which also occurs not uncommonly as the result of the infection without the use of roentgen rays. I think there should be some distinction in the selection of the type of roentgen treatment used. If the involvement is of the superficial type with little induration in the skin, unfiltered irradiation is adequate. If the involvement is of the type with which considerable thickening is present, then adequate filtered radiation should be employed.

A Case for Diagnosis (Sarcoid?). Presented by DR. H. N. KLEIN, St. Paul.

About eight months ago the patient noticed a bright red spot about the size of a dime near the outer canthus of the right eye. At first it was scaly, but later the surface became smooth and more livid. The lesion grew peripherally and above the level of the skin, resembling a flat plateau; it was firm and nodular on palpation and not freely movable above the underlying tissue. For the last three months it has remained the same in size and appearance. A tentative diagnosis of sarcoid was made.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: This lesion is unusual and rather difficult to analyze. I cannot make a clinical diagnosis. I do not believe the lesion is a sarcoid, because a sarcoid is of a different color and consistency and fades off into the surrounding skin, and usually the center of the lesion is depressed. I think this is some sort of inflammatory growth, and I believe that it has some clinical characteristics of epithelioma. Certainly a biopsy will be necessary to settle the diagnosis.

DR. J. F. MADDEN, St. Paul: When the tissue was cut for a biopsy, it had a hard, fibrous feel, which, in my mind, eliminated the possibility of epithelioma.

A Case for Diagnosis (Atopic Eczema? Corneal Ulcers with Beginning Cataracts?). Presented by DR. J. F. MADDEN, St. Paul.

G. E., a white youth aged 19, stated that he had eczema from infancy until he was 6 years old. The eruption disappeared for ten years and recurred in 1937

accompanied by visual disturbances. The patient steadily lost vision. At present there is a great deal of corneal scarring and the patient has about 20 per cent of normal vision. The entire skin is hyperpigmented. The face, the neck and the cubital and popliteal spaces are lichenified. There is a weeping, crusted, vesiculopustular dermatitis involving the face, neck and cubital and popliteal spaces. The patient also has hay fever, and his grandfather had asthma. He has been under the care of many competent dermatologists and allergists throughout the Northwest.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: I am constantly discussing the problem of atopic dermatitis with a group in the clinic, and to me this is a problem which warrants the provoking of much public opinion, so that atopy may become a problem in which the government will be interested.

DR. L. A. BRUNSTING, Rochester: The occurrence of cataracts is a serious complication of neurodermatitis. I do not recall having seen any corneal ulcers in cases of this disease, but occasionally there is found detachment of the retina, which may be evident only after the cataract has been removed surgically. Of the many explanations which have been given for the cause of the syndrome of neurodermatitis, none is satisfactory. I lean toward a disturbance of the parasymathetic-sympathetic mechanism and believe that hypersensitivity is only one expression of this change.

A Case for Diagnosis (Schamberg's Disease? Pigmented Purpuric Lichenoid Dermatitis?). Presented by DR. J. F. MADDEN, St. Paul.

Mrs. H. C., a white woman aged 53, stated that an eruption appeared on her thighs in 1939 and now is scattered on the legs and trunk. The eruption appears as irregular, asymptomatic, maculopapular, reddish yellow, cayenne-pepper-like, dime-sized to dollar-sized patches. The Wassermann reaction was negative.

Schamberg's Disease. Presented by DR. J. F. MADDEN, St. Paul.

A. D., a white man aged 41, was admitted to the Ancker Hospital because of chronic alcoholism, convulsions thought to be due to alcoholism and hepatomegaly with questionable cirrhosis of the liver. During the course of his examination, yellowish brown, macular patches resembling cayenne pepper were noticed on the skin of his legs from the knees to the ankles. There are no subjective symptoms. There is no associated edema or varicose veins. The eruption has been present since about 1931.

DISCUSSION OF TWO CASES OF SCHAMBERG'S DISEASE

DR. E. A. STRAKOSCH (by invitation), Minneapolis: I believe that Schamberg's disease and pigmented purpuric lichenoid dermatitis belong in the same group. The pathologic changes in both conditions are the same. To my way of thinking, they are only different stages of the same disease.

DR. C. W. LAYMON, Minneapolis: I think Dr. Strakosch is correct. Gougerot and Blum came to the same conclusion—that both are forms of stasis dermatitis. Schamberg's disease as well as pigmented purpuric lichenoid dermatitis appear most frequently on the legs, and in most cases there are varicosities. When Dr. Michelson and I studied pigmented purpuric lichenoid dermatitis we often differed in the diagnosis of conditions which were either Schamberg's disease or pigmented purpuric lichenoid dermatitis, and we agreed that differentiation between the two conditions is often difficult. The alleged characteristic lesion in pigmented purpuric lichenoid dermatitis is a small shiny orange papule.

DR. J. F. MADDEN, St. Paul: I could never see any difference between the microscopic sections of Dr. Laymon's cases presented as instances of purpuric

lichenoid dermatitis and those of Schamberg's disease. It has always been my opinion that these two names represent the same disease.

Cutis Hyperelastica. Presented by DR. J. F. MADDEN, St. Paul.

D. A., a boy aged 8 years, since infancy seemed to have very tender skin which was easily injured. He is one of eight children, three boys and five girls, and none of the other children has any cutaneous abnormality. None of his ancestors was known to have had similar trouble. Each time the patient received an injury or bump a tumor developed at the site of injury. These lesions were marble sized to egg sized, painless and most numerous on the shins, elbows and chin. Some of the lesions ulcerated, while others did not. Flat, soft, painless tumors and scars remain at the sites of previous injuries. The patient can hyperextend his joints to a marked degree. The skin is hyperelastic at all points.

DISCUSSION

DR. C. W. LAYMON, Minneapolis: This case seems to present a nutritional problem. There is hyperelasticity of the skin on the arms and legs.

A Case for Diagnosis (Xanthoma Tuberosum? Xanthelasma?). Presented by DR. J. F. MADDEN, St. Paul.

A. S., a white man aged 59, stated that a nodule appeared on the medial surface of the right index finger at the base of the nail about December 1939. The lesion has grown constantly until it is now the size of a large marble. The nodule is lobulated, orange and painless. The patient also has two irregular, flat, yellow, asymptomatic, millet seed–sized maculopapules on the lower eyelids. The Wassermann reaction was negative. The fasting blood sugar content was 112 mg. per hundred cubic centimeters, and the blood cholesterol content 250 mg. per hundred cubic centimeters.

DISCUSSION

DR. L. A. BRUNSTING, Rochester: The patient has xanthelasma and perhaps on the index finger a xanthoma of the tendon sheath. In all cases of this type one should search for evidence of cardiovascular disease.

DR. L. H. WINER, Minneapolis: I do not think the condition is xanthoma. I agree with the diagnosis of a lesion of a synovial membrane of the finger tip. The histologic section, being stained with hematoxylin and eosin, shows no cellular cavitation as if fat had been present.

Acne Varioliformis. Presented by DR. J. F. MADDEN, St. Paul.

Mrs. S. S., a white woman aged 38, stated that the eruption on her face and scalp appeared in 1935. The eruption has never entirely disappeared. She now has pinhead-sized papulopustules scattered throughout the scalp. The greatest number are at the hair line, although there are occasional lesions on other parts of the face. Some of the lesions have undergone central necrosis and are covered with a crust. There are numerous associated pinhead-sized pitted scars. The Wassermann reaction was negative. Roentgenograms of the chest were normal. A Mantoux test gave a 2 plus reaction.

DISCUSSION

DR. R. R. KIERLAND, Rochester: At the Mayo Clinic there are no particular words of wisdom concerning the treatment of acne varioliformis. I think definitely that the majority of patients can be materially helped, although a permanent cure is difficult to obtain and patients are not encouraged to hope for this. Ordinarily ammoniated mercury is used, and it has been my experience that this ointment can be applied in greater strength in the treatment of the scalp than is possible in other regions on the body. More recently sulfathiazole ointment has been used,

and in an occasional case there has been some definite success. Chlorhydroxyquinoline (quinolor) ointment can be used also with much benefit. In cases of the more severe conditions in which no results are obtained with the former measures, neoarsphenamine is given intravenously, and occasionally in conjunction with this typhoid vaccine is administered intravenously for its nonspecific protein effect.

A Case for Diagnosis (Lymphoblastoma?). Presented by DR. J. F. MADDEN, St. Paul.

E. L. a woman, aged 28, was presented before this society in October 1939 (ARCH. DERMAT. & SYPH. **41**:623 [Jan.] 1940) and in October 1940 (*ibid.* **43**:734 [Jan.] 1941). There are no new lesions. The results of laboratory tests are the same. All lesions received a similar amount of roentgen ray therapy. The lesions from which specimens for biopsy were taken have cleared.

DISCUSSION

DR. L. H. WINER, Minneapolis: My impression is that the condition is a mycosis fungoides. I did not see the most recent section of these lesions.

DR. C. D. FREEMAN, St. Paul: Is there anything in a section that can be diagnostic of mycosis fungoides?

DR. L. H. WINER, Minneapolis: Yes. Mycosis fungoides has characteristic cells, large monocytes which are most frequently seen in the tumor stage rather than in the infiltrating stage. In the infiltrating stage a preponderance of eosinophils is seen. One can differentiate mycosis fungoides from Hodgkin's disease by the fact that in Hodgkin's disease more fibroblasts and a greater tendency to fibrosis are seen. In both there are round cell infiltration and eosinophils. Definite criteria for a diagnosis are derived from a study of the histologic picture as a whole and not of the individual components.

DR. C. W. LAYMON, Minneapolis: The patient has had the disease for about five years, and the entire eruption has been limited to not more than twelve lesions, which have not grown to any great extent. Clinically it seems difficult to consider mycosis fungoides, and histologically the lesions have never had definite characteristics of this disease. Dr. Montgomery mentioned the possibility of atypical hemorrhagic sarcoma from sections he examined. The lesions also seem to fit that diagnosis better from a clinical standpoint.

DR. J. F. MADDEN, St. Paul: All of the lesions received approximately the same amount of roentgen therapy. However, only those from which specimens for biopsy were taken have healed.

Lichen Planus Erythematosus. Presented by DR. J. F. MADDEN, St. Paul.

E. W., a white man aged 61, stated that an eruption appeared on his chest about 1938. This has spread until most of the trunk, groin and thighs are involved. There is a distinct ring of normal skin around both nipples. The axillas and the skin directly over the lumbar and dorsal portions of the spine are free from lesions. The eruption is symmetric and accentuated over the shoulders, chest and waistline. On the chest and shoulders there are confluent yellowish red plaques the size of oranges or larger. As the eruption progresses laterally it becomes papular. The papules are uniform millet seed sized and vary from yellowish red to purple. There has been a progressive increase in the number of lesions, and none of them has disappeared. The Wassermann reaction was negative.

DISCUSSION

DR. C. W. LAYMON, Minneapolis: There have been less than half a dozen cases of lichen planus erythematosus reported in the literature. In the first of Crocker's 2 cases the lesions were limited to the groin and face, while in the second they were generalized. The histologic picture is that of lichen planus of the atrophic type.